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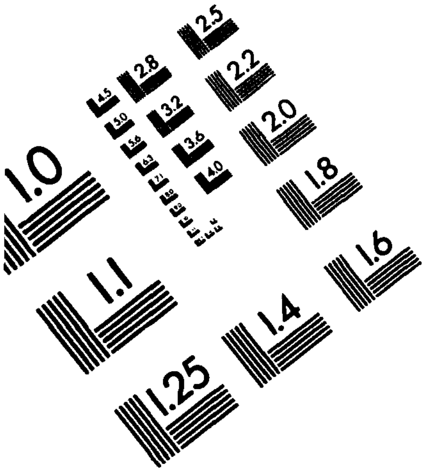

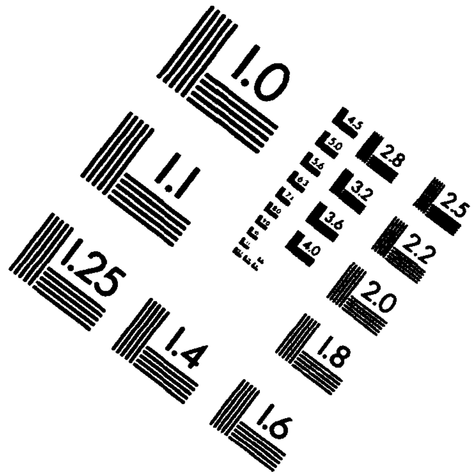

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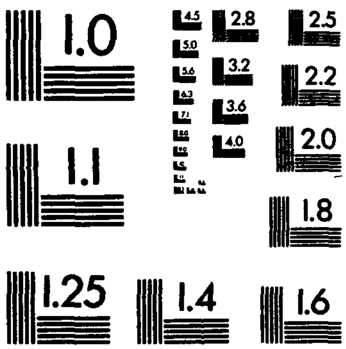

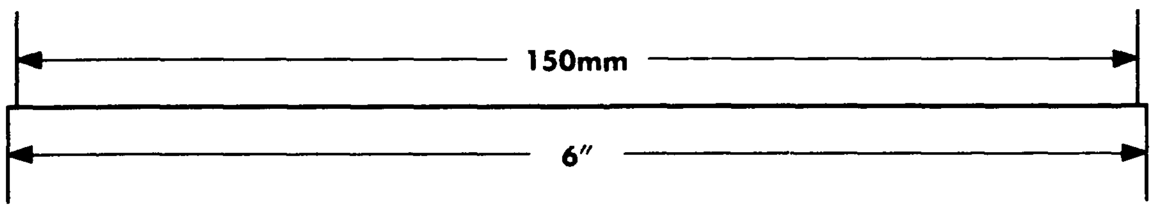

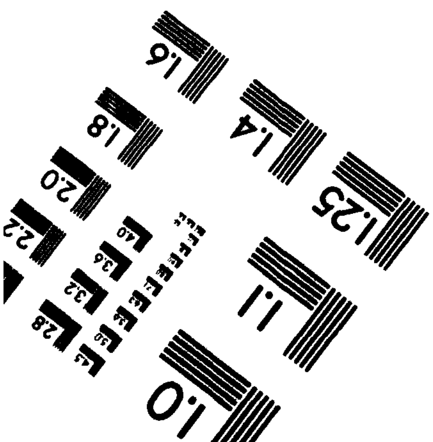

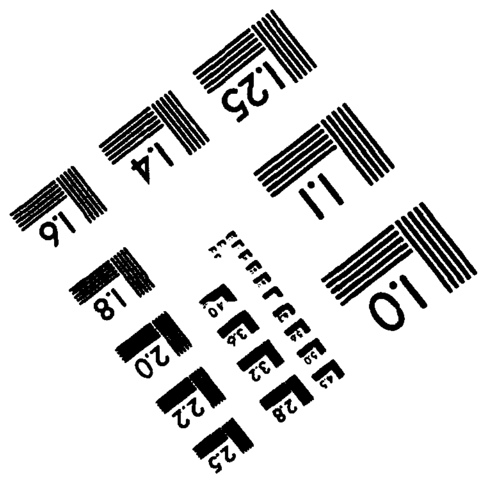

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TESTING OF EXPERIMENTAL COMPOUNDS FOR EFFICACY AGAINST <u>LEISHMANIA</u>

Final Report

William L. Hanson, Virginia B. Waits, and Willie L. Chapman, Jr.

October 31, 1990

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19. ABSTRACT *(Continue on reverse if necessary and identify by block number)*

A total of 1,684 compounds was studied for antileishmanial activity against Leishmania donovani in hamsters. Ninety of these had some suppressive activity, five had activity greater than the reference compound, Glucantime, five had activity approximately equal to that of Glucantime, and the remainder were less active than Glucantime. Several chemical classes including 8-aminoquinolines, purine analogs, quinolines, pyridines, heavey metal complexes, berberine derivatives, and pyrazine or quinazoline inhibitors of dihydrofolate reductase, were among those compounds tested. Some of the 8-aminoquinolines as well as some of the purine analogs were among the most active compounds studied but many were toxic. Quinolines, pyridines, and heavy metal complexes (for example sulfonamides) were active while pyrazine or quinazoline inhibitors of dihydrofolate reductase were generally inactive. Three berberine derivatives had some activity against L. donovani but were generally toxic and less active than Glucantime.

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18. SUBJECT TERMS (Continued)

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pyridines
dihydrofolate reductase inhibitors

A comparison of the efficacy of selected compounds known to be active based on previous studies in this laboratory as well as others showed that the activity of amphotericin B (I.V.) > formycin B (orally) > formycin A (orally) > pentamidine (I.M.) > 3-deazaguanosine (orally) > 9-deazainosine (orally) > allopurinol (orally). In another similar experiment WR06026 > sinefungin > amphyotericin B > Glucantime > 9-deazainosine > pentamidine. Many of these were toxic at dosage levels effecting 90-100% parasite suppression in the liver.

When sinefungin was combined in the treatment of hamsters with _L. donovani_ with each of six purine analogs previously found to be active, no antiparasitic activity greater than that attributable to sinefungin alone was noted. Liposome encapsulation resulted in enhanced antileishmanial activity and lower toxicity of Glucantime, pentostam, formycin B, and amphotericin B when used to treat hamsters and/or monkeys infected with _L. donovani_.

WR06026 and several other 8-aminoquinolines were generally equally active against liver parasites when administered either orally or intramuscularly to hamsters infected with _L. donovani_. Analogs of WR06026 were not as active against hepatic parasites as was WR06026. Both WR06026 and most analogs were more active against extrahepatic parasites when administered orally. WR06026 was active in hamsters when given as a single dose three days prior to infection but was more active when given after infection. WR06026 was highly active against _L. donovani_ in the liver of squirrel monkeys when given at total dosages of 120, 60, or 15 mg/kg body weight. No effect was seen on parasites in the bone marrow of these non-human primates.

9-deazainosine was active against _L. donovani_ in the liver, spleen, and bone marrow of squirrel monkeys at total dosages of 1400 and 350 mg/kg. Fatty livers apparently resulted from this treatment suggesting this compound was toxic at effective dosage levels.

A total of 410 compounds were studied for suppressive activity against cutaneous lesions caused by _Leishmania braziliensis panamensis_ in hamsters. Forty-one of these were noted to suppress cutaneous lesions at least 50% or more. Sinefungin and WR06026 were the two most active compounds against _L. b. panamensis_ with activity ranging from 12 to 30 times that of Glucantime. One other compound had suppressive activity approximately equal to that of Glucantime while two others were approximately one-half as active as Glucantime. Amphyotericin B was only marginally active when administered by the intravenous route. Formycin B was active but was toxic. Allopurinol and formycin A were not active when administered _via_ the intravenous route.

Berberine and 8-cyanodihydroberberine were approximately as active as Glucantime against _L. b. panamensis_ in the hamster.

During the extension period several types of experiments were conducted. A total of 17 compounds were studied for activity against _L donovani_ and none were active. No enhancement of parasite suppression was noted in hamsters receiving the combination of oxyformycin B and sinefungin when compared to those hamsters receiving sinefungin alone. Neither paromomycin, neomycin, or gentamycin were active against _L. donovani_ when administered intraperitoneally alone or in combination. Liposomal muramyl tripeptide (MTP) in combination with Glucantime showed little improvement in antileishmanial efficacy against _L. donovani_ when compared to that of Glucantime alone. MTP was toxic to the treated hamsters. Sinefungin had similar activity when a total dosage of 52 or 6.25 mg/kg was administered in one, two, four, or eight treatments. When a total dosage of 3.25 mg/kg was used, parasite suppression was enhanced concurrently as the number of treatments were increased.

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

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_____For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45 CFR 46.

_____In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

PI Signature William L. Hanson Date October 31, 1990

TABLE OF CONTENTS

TABLES

FIGURES

INTRODUCTION

(Statement of the Problem and Background)

The leishmaniases, the group of diseases caused by protozoan parasites of the family Trypanosomatidae, genus *Leishmania*, are widely distributed throughout the world and are found on every inhabited continent except Australia (Kinnamon *et al*., 1). These diseases occur in such important countries as Russia, China, India, Pakistan, Egypt, Sudan, Israel, Syria, Iran, Saudi Arabia, Brazil, Venezuela, Panama, Mexico, Argentina, and many others. These parasites are transmitted by several species of phlebotomine flies and in most areas the leishmaniases are zoonoses with canines, rodents, or other mammals serving as reservoir hosts.

These parasites are a significant health hazard to humans in these areas. Visceral leishmaniasis, the most severe type, is endemic in many areas where epidemics occur (TDR Publ., 7th Program Rpt., 2) with mortality reported to reach as high as 98 percent in untreated cases (Biagi, 3; Steck, 4). While it is difficult to obtain an accurate estimate of the number of human beings infected with the leishmaniases throughout the world (TDR Publ., 7th Program Rpt., 2), some estimates indicate that at least 12 million persons have one of the different forms of the disease caused by infection with these parasites (Mahmoud and Warren, 5; Croft, 6) and outbreaks often involving additional thousands of persons occur periodically (Peters, 7; TDR Publ., 7th Program Rpt., 2; Perea, 8). Some believe as many as 2 to 3 million new cases per year occur worldwide (Croft, 6).

Infection with these parasites represents a significant health hazard to military personnel operating in many areas of the world. For example, during World War II where troops were operating in an endemic area of the Persian Gulf, 630 cases were reported in a three-month period (Most, 9). Subsequently during troop movements in another endemic area, 50 percent of certain Israeli forces experienced infections (Naggan *et al*., 10). In addition, although relatively few troops were involved, 10 to 45 cases per year have been reported among U. S. troops in the Canal Zone (Walton *et al*., 11) and a subsequent report indicated an overall infection rate of 1.6% in one U. S. Army battalion that was deployed to Fort Sherman in the Canal Zone for jungle warfare training (Takafuji et al., 12). Although mortality may occur, the primary problem is the considerable loss in duty time in infected individuals. For example, it has been estimated, that each individual having visceral leishmaniasis lost at least one year duty time (Most, 9) and in one instance in which 20 cases of cutaneous leishmaniasis occurred in troops in the Canal Zone, two man-years of duty time were lost (Walton *et al*., 11).

While chemotherapy is currently the only practical means of treatment for these parasites, it has not been consistently successful (Neal, 13; Croft, 6). The first line drugs currently available to treat the leishmaniasis are the pentavalent antimony compounds (Neal, 13; Bryceson, 14). While these drugs are less toxic than previously believed (Bryceson, 14), they have significant limitations in that they must be administered *via* the parenteral route and often repeated injections are required. In addition, these compounds are often not curative and evidence of antimony resistance among the *Leishmania* is increasing. For example, a strain of *L. donovani* from Kenya has been shown to be considerably more insensitive to antimony than a strain which has been in the laboratory for many years (Hanson *et al*., 15), and reports of leishmaniasis in humans unresponsive to pentavalent antimony therapy are reasonably common (Mebrahtu *et al*., 16). Furthermore, antimony resistant strains of *L. donovani* and *L. braziliensis panamensis* have been developed experimentally in this laboratory (Waits *et al*., unpublished). Other evidence for the presence of drug resistance among the *Leishmania* has been reviewed by Croft (6). The backup drugs for treatment of the leishmaniases, amphotericin B or pentamidine, have even more problems in that they cause adverse effects in humans as a result of toxicity (see Jackson *et al*. for references, 17).

The current prospects for new drugs for the treatment of visceral leishmaniasis are quite limited (WHO Publication, 18; Neal, 13; Croft, 6). Drugs with proved efficacy in laboratory animals and which are currently undergoing pre-clinical or clinical studies are WR06026 and allopurinol riboside. Drugs or delivery systems in various stages of development and showing some promise are sinefungin, formycin B, miconazole, and liposomes. Formycin B has been observed in this laboratory to be extremely toxic in dogs and only marginally active and thus additional study of this compound is probably not warranted. In our experience sinefungin is also toxic and this toxicity probably will preclude further consideration of this compound for future practical use. Considerable work remains to be done before any of the others will be useful on a practical basis. Furthermore, the possibility that Leishmania already exists which are resistant to WR06026 (an 8-aminoquinoline) must be considered since these infections occur in areas of the world where 8-aminoquinolines have been used against malaria in humans.

Because of the potential importance of the leishmaniases to the health and performance of military personnel in many parts of the world and the need for improved and more satisfactory chemical compounds for consistent successful treatment of these diseases, this project was initiated to test experimental compounds for efficacy against Leishmania donovani and L. braziliensis panamensis infections in the golden hamster as the primary test systems and in non-human primates as a secondary test system. This is the final progress report for this project and covers the period 1 January 1985 through 30 June, 1990. Due to the fact that a separate report for the extension period (1 January 1990 - 30 June 1990) was not filed, this final report includes a clear and distinct section for work performed during this interval. This report describes the test procedures used and summarizes the results obtained. The test results obtained have been sent to appropriate officials at The Walter Reed Army Institute of Research as they became available during the contract years.

MATERIALS AND METHODS

(Approach to the Problem)

I. Studies Involving *Leishmania donovani*

A. *In Vivo* Studies Using the Hamster Model

1. Primary Visceral Test System

A Khartoum strain of *L. donovani* (WR378) was used and male golden hamsters (*Mesocricetus auratus*), 50-70 gm, served as the host animals. Suspensions of amastigotes for infection of experimental hamsters were prepared by grinding heavily infected hamster spleens in sterile saline in a Ten Broeck tissue grinder and diluting the suspensions so that 0.2 ml contained approximately 10×10^6 amastigotes. Each experimental hamster was infected *via* the intracardiac injection of 0.2 ml of the amastigote suspension.

The testing procedure used was that described by Stauber and his associates (19, 20, 21) as modified by Hanson *et al*. (22). On day 3 following infection, hamsters were divided randomly into experimental groups consisting of a minimum of 6 animals per group, initial group weights were obtained, and administration of test compounds was initiated. Each compound was tested at 2 or 3 drug dosage levels dependent on the priority rating of the compound. Generally the test compounds with high priority ratings were studied initially *via* the intramuscular route (I.M.) at total dosages of 416, 208, and 52 mg/kg (milligrams/kilogram) while those compounds received with a routine or low priority rating were studied at 208 and 52 total mg/kg only. Other drug dosage levels determined by the quantity of compound available or previous toxicity data were used also.

The vehicle for the test compounds was 0.5% hydroxethylcellulose-0.1% Tween 80 (HEC-Tween). Each test group contained 6 hamsters and received one of the desired drug dosage levels. A control group of 6 to 8 hamsters received the 0.5% HEC-Tween vehicle only and the reference compound, Glucantime®, was given at 2 or 3 drug dosage levels (208, 52, and 26 total mg/kg or 208 and 52 total mg/kg based on antimony content). All test compounds were administered routinely twice daily *via* the intramuscular route on days 3 through 6. Final group weights were obtained on all experimental hamsters on day 7 and all animals were killed, livers removed, weighed, and liver impressions made for enumeration of amastigotes. Subsequently, the total number of parasites per liver was determined as described by Stauber (20).

In addition to recording body weight changes as a general indicator of toxicity of the test compounds, experimental hamsters were observed for such clinical signs of toxicity as nervous disorders, roughened hair coat, and sluggish activity. Deaths also were recorded. Weight loss of 15% or greater and/or death of the animals was considered indicative of significant drug toxicity.

After determining the ratio of numbers of amastigotes/host cell nucleus, the weight of the organ, and initial and final weights of the hamster, the raw data was evaluated with an IBM PC XT microcomputer using a program which calculates percent weight change, total numbers of parasites, mean numbers of parasites/organ, and percent parasite suppression. The computer program then performs linear and non-linear regression analysis and calculates a SD_{50} for each active compound from each of the analyses (drug dosage resulting in 50% suppression of amastigotes). The SD_{50} from the non-linear analysis is used for a comparison of the relative efficacy of the test compounds and the efficacy of test compounds relative to that of the reference compound, Glucantime. The linear regression analysis is included in the program only for comparison with the non-linear analysis.

Additional information on the antileishmanial activity of each active compound was obtained by comparing the percent suppression of number of amastigotes it exhibits with the percent suppression observed with Glucantime, the reference compound. This comparative measure (referred to as the Glucantime Index or "G") was determined by the following formula:

$$\text{Glucantime Index} = \frac{SD_{50} \text{ for Glucantime}}{SD_{50} \textit{ for new test compound}}$$

2. Special Cooperative Studies

As detailed in Memorandum for the Record, SGRD-UWM dated 7 June 1984, (Division of Experimental Therapeutics, WRAIR) a series of experiments were carried out during this project period on carefully selected compounds, many of which were either known to have in vivo antileishmanial activity or were suspected of having in vivo antileishmanial activity because of positive data from in vitro studies. The compounds studied were as follows: allopurinol, 9-deazainosine, 3-deazaguanosine, pentamidine, formycin A, formycin B, amphotericin B, ketaconazole, 6-mercaptopurine riboside, adenosine, nalidixic acid, novobiocin, aphidicolin, 4-mercapto-1H-pyrazolo - [3,4-d] pyrimidine, glycolate ester, WR251815, WR248829, WR248830, WR250297, WR253563, WR253554, WR253549, WR253556, WR250678, and WR23[illegible]91.

Procedures used for this experiment (parasite, 3 day infection, killing of hamsters, and enumeration of parasites) were similar to those used for the primary visceral screen. Route of administration of the test compounds varied according to compound; the most efficacious route being used. Results were evaluated using a microcomputer program.

3. Liposome Studies in Hamsters

Neat and liposome encapsulated amphotericin B, formycin B, Pentostam and Glucantime were studied in hamsters infected with L. donovani using procedures similar to those used for the primary visceral test system. All liposome preparations and neat amphotericin B were administered intracardially in a single injection, neat formycin B was given orally in a single dose, and neat Pentostam and Glucantime were administered intramuscularly in a single injection. At the termination of the experiment, the hamsters were killed, spleens and livers were removed, and impressions made for the enumeration of parasites as described for the primary test system. Results were evaluated using a microcomputer program as described in the preceding section.

4. Efficacy of WR06026

A. Analogs

The antileishmanial efficacy of 17 analogs of WR06026 (BK90014, BL058884, BL18736, BL18765, BK40735, BK50713, BK56573, BK56733, BL24361, BK99014, BL31839, BL34296, BL34296, BL52196, BL52749, BL52954, and BL53308) was compared to that of WR06026 (BK01845) in seven separate experiments. The strain of Leishmania, experimental animals, infection of experimental hamsters, the killing of hamsters (Day 7), preparation of impression smears, the quantitation of amastigotes, toxicity evaluation, and the evaluation of raw data was the same as that described in the preceding section I.A.1 (Primary Visceral Test System). In all experiments, WR06026 served as the reference compound.

Various routes and regimens were used in these experiments. BK90014 and BL05884 as well as WR06026, Glucantime, and vehicle were administered to experimental hamsters twice a day for 4 days (Days 3-6). The route of administration was either orally or intramuscularly as warranted for the test groups. BL18736 and BL18765 along with WR06026 were administered via the

intramuscular route in some groups and oral route in others twice each day for 4 days (Days 3-6). Six analogs (BK40735, BK50713, BK56573, BK56733, BL24361, and BK99014) along with WR06026 were administered via the intracardiac route as a single injection on day 3 following infection.

Two experiments were conducted in which the efficacy of BL31839, BL34296, BL52196, BL52749, BL52954, and BL53308 was compared to that of WR06026. In the first experiment a total of 203 infected hamsters was divided into 29 groups containing seven hamsters per group and the test compounds were administered to appropriate groups of hamsters via the intracardial route once only on day 3 postinfection. Control groups received WR06026 at total dosages of 1.6, 0.4, 0.1, or 0.025 mg/kg. The analogs were administered to groups of hamsters at the same total dosage levels as WR06026.

In the second experiment a total of 174 infected hamsters was divided into 29 groups consisting of 6 hamsters per group. WR06026 again served as the reference compound and this compound or the appropriate analog was administered at appropriate dosages as a single treatment on day 3 of the infection via the oral route. The dosage levels of WR06026 and the six analogs used were 1.6, 0.4, 0.1, or 0.025 mg/kg.

The remaining analog, BL34296, and analog, BL31839 (investigated in the experiments above) were studied in two separate experiments. In one experiment a total of 60 infected hamsters was divided into 10 groups containing six hamsters per group and the test compounds were administered to appropriate groups of hamsters via the intramuscular route twice daily for four days. Control groups received WR06026 at total dosages of 0.812, 0.2132, or 0.0508 mg/kg. The analogs BL31839 and BL34296 were administered to groups of hamsters at total dosages of 3.25, 0.812 or 0.2032 mg/kg.

In the second experiment a total of 133 infected hamsters was divided into 19 groups consisting of 7 hamsters/group. WR06026 again served as the reference compound and this compound or the appropriate analog was administered at desired dosages as a single treatment on day 3 of the infection via the intracardial route to 9 of the groups with an additional group receiving vehicle only via this route. The remaining 9 groups received WR06026 and the analogs via the oral route as a single treatment on day 3. The dosage levels of WR06026 used for either route of administration were 0.4, 0.1, and 0.025 total mg/kg and the dosage levels of the analogs used for either route of administration were 1.6, 0.4, and 0.1 total mg/kg.

B. Efficacy of WR06026 when Administered Prior to Infection.

During three years of this contract period, a series of studies was conducted in which WR06026 and five analogs of WR06026 were administered to hamsters prior to infection with L. donovani. Hamsters were treated either 3, 2, or 1 day prior to infection (in one experiment on 3, 2, and 1 day prior) while control hamsters were treated on Day 3 subsequent to infection. All test compounds were administered orally and hamsters killed on Day 7 post-infection. Procedures for infection, quantitation of amastigotes, and evaluation of efficacy were the same as described for the primary visceral test system.

5. Optimization Study of Selected 8-Aminoquinolines

The effect of route of administration on efficacy against L. donovani was determined for six 8-aminoquinolines (BL51297, BL50021, ZP45845, BK84200, BK99121, and BL03308). Infection, treatment, and necropsy were performed according to the schedule for routine primary screening; however, 3 dose levels were used for each compound and compounds were administered either orally or intramuscularly.

6. Comparison of the Efficacy of Selected Compounds Against *L. donovani*.

A comparison of the efficacy of sinefungin, 9-deazainosine, pentamidine, amphotericin B, WR06026, and the reference compound, Glucantime, was done using procedures outlined for the routine primary visceral test system (Sec. I.A.1.) with the following modifications.

Compounds in this experiment were administered *via* the route determined to be the most efficacious during previous studies (i.e., Glucantime, sinefungin, and pentamidine *via* the intramuscular route, 9-deazainosine and WR06026 *per os*, and amphotericin B *via* the intracardiac route). All of this group of compounds were administered twice each day on days 3-6 after infection except amphotericin B which was given once daily during this interval. The dosage levels used were determined from data obtained from prior studies of these compounds in the primary visceral test system.

7. Combination Studies

A single study was performed to determine the effects of combined treatment with sinefungin (WR254847) and each of 6 purine analogs that had previously been found to be active against *L. donovani* infection in our model system. Animals were infected, treated, and necropsied according to the schedule routinely used for the primary visceral screening model. Each treatment consisted of indicated doses of sinefungin administered intramuscularly and one of the purine analogs administered *per os* by gavage, these routes having been proven to be optimal for these types of compounds in previous experiments. Dose levels were selected based upon previous results to be in the range of the SD_{50} for sinefungin and below the SD_{50} or below the toxic dose for the purine analogs.

8. Studies with Derivatives of Berberine.

The quaternary alkaloid, berberine, and eight of its derivatives were tested for efficacy against *L. donovani*. Procedures used were the same as those described for the primary visceral test system.

B. *In Vivo* Studies Using the Monkey Model

1. Liposome Study in Monkeys

Young adult squirrel monkeys (*Saimiri sciureus*) were used in this experiment. They were obtained from Charles River Research Primate Corporation, P. O. Box 416, Washington, NY 11050. All except 2 were males. Two females were included to evaluate the toxicity and possible efficacy of "empty liposomes" because of the unavailability of additional males. Upon arrival in the laboratory the monkeys were checked for the presence of parasites, treated for intestinal nematodes, and each was skin tested in the right eyelid with 1×10^6 killed promastigotes of *L. donovani* to determine previous contact with *Leishmania*. All monkeys were skin test negative.

Monkeys were infected with approximately 10×10^7 amastigotes of *L. donovani* per kg body weight obtained by grinding heavily infected hamster spleens in a Ten Broeck tissue grinder and diluting this homogenate with saline to a final concentration of 10×10^7 amastigotes/ml. Each monkey was infected intravenously based upon weight (i.e., a monkey weighing one kilogram received 1.0 ml or 10×10^7 amastigotes).

On day 17 post infection, treatment was begun using liposome encapsulated amphotericin B, neat amphotericin B, Glucantime, "empty liposomes", or saline (vehicle control). The treatment regimen varied from a single injection (saline and liposome encapsulated amphotericin B) every three

days (neat amphotericin B; liposome encapsulated amphotericin B), or once a day for 7 days (Glucantime). All preparations were administered via the intravenous route except Glucantime which was given via the intramuscular route.

Blood samples were obtained from each monkey prior to infection, prior to initiation of treatment, as death occurred when possible, and from survivors when the experiment was terminated (Day 27 post infection). A blood sample was submitted for hematology and the remainder allowed to clot, serum collected, and stored at -80C, and was forwarded to WRAIR for analysis. A complete necropsy was performed on all monkeys and samples from all major organs were fixed in 10% buffered formalin and processed for histological examination. Gross lesions were recorded at necropsy. Numbers of amastigotes were quantitated from impressions of the liver and spleen (as previously described for the hamster), and the number of amastigotes/1000 host cell nuclei was determined from bone marrow preparation of each monkey.

2. WR06026 Study in Monkeys

Adult squirrel monkeys used in this experiment were obtained from South American Primates, Inc., Miami, Florida and from the Center for Disease Control, Atlanta, Georgia. The monkeys were adults and of both sexes.

Acclimatization and skin testing for Leishmania were the same as that described in the preceding section. Each experimental group contained two males and one female.

Treatment was initiated on Day 17 postinfection and continued for 10 days. Dosage levels of 120, 60, 15, 3.75 and 0.94 total mg/kg of WR06026 were used. Three monkeys received vehicle only as controls. Numbers of amastigotes in the liver, spleen, and bone marrow were determined and mean percent suppressions determined as described in the preceding section.

3. 9-deazainosine Study in Monkeys

Young adult, male squirrel monkeys obtained from Charles River Research Primate Corporation were acclimatized and skin tested as previously described.

Treatment was initiated on day 17 postinfection and administered once a day for seven consecutive days. 9-deazainosine was given orally to groups of three monkeys each at 1400 and 350 total mg/kg while Glucantime was administered intramuscularly at 364 and 91 total mg/kg. Three monkeys received vehicle only via the intramuscular route. Blood samples were obtained from monkeys receiving vehicle only and 1400 mg/kg of 9-deazainosine prior to infection, prior to initiation of treatment, and at necropsy. Blood samples were collected and hematology assays performed. A complete necropsy of these 6 monkeys was performed and samples from selected organs fixed in buffered formalin and processed for histopathologic examination. Gross lesions were recorded at necropsy. Numbers of amastigotes in the liver, spleen, and bone marrow were calculated and mean percent suppressions calculated as described in the preceding section.

C. In Vitro Studies

Due to some potentially promising compounds being available in minute quantities, efforts were made during this contract to establish an in vitro test system for L. donovani in this laboratory. The mouse macrophage in vitro test system described by Neal and Croft (23) with some modification served as the basis for these studies. Macrophages of varying numbers were plated into microtiter plate wells or wells incorporated into Lab-Tek chamber slides. Macrophages were infected with various ratios of parasite to macrophage (1:1 to 10:1) using amastigote or promastigote forms. Glucantime was used as the reference compound.

II. Studies Involving *Leishmania braziliensis panamensis* Using the Hamster Model

A. Confirmation of Validity of Cutaneous Test System

A total of 250 hamsters were inoculated with *L. braziliensis panamensis* as described for the primary cutaneous test system. Approximately one-half of these were maintained without chemotherapy and the hair was removed from the lesion area by the weekly application of a commercial depilatory agent. Three or four of these hamsters were killed each week for 14 weeks following infection and lesions measured, excised, weighed, ground in 0.9% saline in a Ten Broeck tissue grinder, and the numbers of amastigotes quantitated using the procedure described by Hanson and Roberson (24). A group of 12 of these hamsters was selected at random and lesion measurements were made at weekly intervals for 20 weeks. Six of these hamsters were killed 2 months after infection and an additional 6 were killed 4 months after infection and spleens homogenized and cultured in Schneider's Drosophilia Medium (Hendricks et al., 25) to check for presence of *Leishmania*. The remainder of the untreated hamsters were held to determine the ultimate fate of the cutaneous lesions.

The other half of the hamsters used in this experiment were divided at random into 18 groups and each group was treated on days 19-22 with either vehicle only, Glucantime administered twice daily at 52 mg/kg body wt/day (MKD), Glucantime administered twice daily at 208 MKD, Glucantime administered twice daily at 416 MKD, Glucantime administered at a total dosage of 208 mg/kg in a single treatment, and Glucantime administered at a total dosage of 832 MKD in a single treatment. Lesion area was determined from six hamsters from each group beginning one week after completion of treatment and continuing for 6 weeks. Three hamsters from each group were killed one week after completion of treatment and another 3 hamsters from each group were killed 7 weeks after completion of treatment. Lesions were measured, weighted, ground in saline, and the number of amastigotes counted as described by Hanson and Roberson (24).

The mean numbers of amastogites per gm of lesion were calculated for the lesions of all experimental groups and the effect of drug treatment on numbers of amastigotes was determined by comparing the mean number in the vehicle group with that of the treated groups. The percent suppression of amastigotes resulting from drug treatment was calculated for each drug dosage level used.

B. Primary Cutaneous Test System

Leishmania braziliensis panamensis (strain WR539) was used in these studies. Male golden hamsters, 50-70 grams, served as experimental hosts.

Promastigotes for establishing experimental infections in hamsters were grown in Schneider's Drosophila Medium (Hendricks et al., 25) and quantitated using procedures described previously (Hanson and Roberson, 24). In preparation for infection and weekly during the experiment, the hair was clipped on the dorsal tail head and a commercial depilatory agent applied to the area to remove the remaining hair. Each hamster was inoculated *via* the intradermal route with approximately 1.5×10^7 promastigotes of *L. braziliensis panamensis* near the base of the tail using a 0.25 ml glass syringe equipped with a 30 gauge x 1/2" needle. Each experimental group consisted of six hamsters. Initial body weights were obtained and administration of therapy, generally *via* the intramuscular route, was initiated on day 19 postinfection, and continued through day 22 postinfection. Glucantime was included at two dosage levels (832 and 208 total mg Sb/kg) as the reference compound and a group of six hamsters received vehicle only (HEC-Tween). Test compounds were administered generally at 416 and 208 total mg/kg.

Lesion area of each experimental hamster was determined with the aid of a template made at WRAIR and calibrated according to the formula $r_1 r_2 \Pi$ where r_1 is the major radius of the lesion and r_2 is the minor radius, (Wilson et al., 26). The mean lesion area of each experimental group was obtained and the percent suppression of lesion size calculated by comparing the mean lesion area of each treated group with that of the group receiving vehicle only with the aid of a computer program and an IBM PC XT microcomputer. The computer program performs linear and non-linear regression analysis and calculates an SD_{50} for each active compound using both analyses. The SD_{50} obtained from the non-linear analyses is used for a rough comparison of the relative efficacies of the test compounds and the relative efficacy of test compounds with that of the reference compound, Glucantime. This may be expressed as the Glucantime Index as described in section I. The liner regression analysis is performed for comparison with the non-linear analysis.

C. Special Cooperative Studies

One experiment was conducted during this project period as a part of the joint effort at a more rational approach to antileishmanial drug studies (detailed in Memorandum for the Record, SGRD-UWM dated 7 June 1984). The procedures used were the same as that for the primary cutaneous test system with the exception of route and regimen. Several of the most promising antileishmanial compounds were selected from those studied as described in a previous section (Special Cooperative Studies, I.A.2). These were allopurinol, formycin A, and formycin B. These compounds were compared for activity when administered either orally or intramuscularly using a bid x 4 day regimen. Amphotericin B was given either intracardially or intraperitoneally in a single injection. Hamsters receiving vehicle only and Glucantime were included as controls. Results were evaluated using a microcomputer program.

D. Studies with Derivatives of Berberine

The quaternary alkaloid, berberine, and eight of its derivatives were tested for efficacy against L. braziliensis panamensis. Procedures used for this study were the same as those for the primary cutaneous test system.

III. Studies Performed During the Extension Period Involving Leishmania donovani

A. Primary Visceral Test System

Procedures used for the completion of routine testing of test compounds on hand were the same as those outlined in section I.

B. Combination Studies

During the extension period of this contract, three experiments were carried out in which experimental hamsters received combinations of known compounds to determine enhancement of the efficacy against L. donovani. Procedures used in infecting the hamsters, quantitation of parasites, determination of drug toxicity, and evaluation of raw data were the same as those used for the primary visceral test system. Exceptions to the procedures for the primary screen are detailed below.

1. Oxyformycin B and Sinefungin

Each group of hamsters contained 7 animals and Glucantime, sinefungin, and oxyformycin B served as the reference compounds. In the experimental groups receiving both oxyformycin B and sinefungin, the dosage level of oxyformycin B was held constant (208 total mg/kg) while that of sinefungin was varied (13, 6.5, 3.25 total mg/kg). Oxyformycin B was administered orally

while sinefungin and Glucantime were given intramuscularly. Animals were treated twice a day for four days beginning on day 3 postinfection and killed one day following completion of treatment.

2. Paramomycin, Neomycin and Gentamycin Sulfate

Experimental groups of infected hamsters received combination treatments of paramomycin and gentamycin sulfate or paramomycin and neomycin twice a day for 4 days beginning on day 3 postinfection. All injections were via the intraperitoneal route. The dosage levels of paromomycin were varied as to concentration (500, 700, or 900 total mg/kg) while the levels on the combining drug was held constant (gentamycin sulfate, 1200 total mg/kg; neomycin, 700 total mg/kg). Glucantime studied at three dosage levels, paromomycin alone at three dosage levels, and gentamycin sulfate alone or neomycin alone at a single dosage level served as the reference compounds. Groups receiving the drug combinations were injected with paromomycin each morning and either gentamycin sulfate or neomycin each afternoon. Reference compound groups received the appropriate drug each morning and were sham dosed with HEC-Tween in the afternoon. All hamsters were killed and impression smears made one day following completion of treatment.

3. Liposomal Muramyl Tripeptide (MTP) and Glucantime

Infected hamsters were divided into groups of 8 animals and initial weights determined (Day 0). Groups were treated according to one of four regimens: a) vehicle only control; b) MTP only; c) Glucantime only; or d) combined MTP and Glucantime. MTP was administered in an intracardiac dose of either 100 or 200 ug (approximately 1.5 and 3.0 mg/kg/day respectively) on each of days 7 and 10. Glucantime was administered intramuscularly in doses of either 13 or 52 mg/kg/day on each of days 8, 9, 10 and 11. Final group weights were determined and animals killed on day 12 for enumeration of amastigote burdens. MTP was suspended in physiologic saline and Glucantime was suspended in HEC-Tween prior to injection.

C. Optimizing Regimen for Sinefungin

In this study, procedures used were the same as those described for the primary visceral test system with the exception of the regimen used. Total dosages of sinefungin (52, 6.5, or 3.25 mg/kg) were administered to groups of infected hamsters either once (Day 3), twice (Days 3 and 5), four times (Days 3, 4, 5, and 6), or eight times (twice a day on Days 3, 4, 5, and 6). Along with sinefungin-treated groups, a vehicle control (HEC-Tween) as well as Glucantime-treated groups (208, 52, or 26 total mg/kg) were included in each of the four regimens used. All compounds and the HEC-Tween control were administered intramuscularly. Animals were killed and impression smears made for enumeration of parasites one day following completion of the final treatment (Day 7).

RESULTS

I. Studies Involving *Leishmania donovani*

A. *In Vivo* Studies Using the Hamster Model

1. Primary Visceral Test System

A total of 1,684 compounds were tested in the primary visceral screening system during the regular contract period. Among those tested, 90 compounds (5.5%) were active. In these studies, test compounds were considered active when they were $\geq$ 50% suppressive at one or more dosage levels used. This level of activity was chosen based on 10 years previous experience with a computer analysis program from which statistical significance was obtained. Generally, parasite suppression of 50% and greater was statistically significant. Amastigote suppression as great as 40% was often not found to be statistically significant in this test system. The results for active compounds are shown in Appendix 1 (Table I) and their structures are illustrated in Appendix 2 (Figure 1).

Compounds found inactive (i.e., <50% suppression) in this test system and listed in Appendix 1, Table II.

Thirty-three of the 90 active compounds were sufficiently suppressive to warrant the calculation of Glucantime Indexes. The activity of five of these was greater than that of Glucantime (BK85510, G=2.62; ZP23714, G=7.88; ZP46833, G=6.61; BL10956, G=14.18; WR06026, G=87.8). The activity of several others was at least as great as that of the reference compound, Glucantime (BL20649, G=1.17; BL09533, G=1.37; BK99121, G=1.38; AJ15304, G=2.58; BH32724, G=2.82). The Glucantime Indexes for the remaining active compounds were less than that of Glucantime.

Several chemical classes are represented among these active compounds. The 8-aminoquinolines BL51297, BL51304, BL50021, BL49993, BH56265, BL52749, BL53308 and ZP30451 were the most potent compounds and also were toxic as evidenced by host mortality at doses $\geq$ 208 mg/kg. Only BL49993 failed to cause mortality at higher dose levels, although an average 16% weight loss was recorded among hamsters receiving 416 mg/kg. The fact, however, that the compounds were 100% suppressive at the lowest dose level tested (52 mg/kg) raises the possibility that these compounds may be highly effective at lower, less toxic doses.

Five inosine analogs were among the active compounds. BL10885 was the most potent with an SD_{50} of 25.2 mg/kg which is roughly one-half that of the average for the reference compound Glucantime. This compound was also very toxic as an average weight loss of 28% was observed among hamsters treated with 52 mg/kg. The toxicity and/or low potency of this group of active compounds disqualifies them from further interest at this time.

Quinolines, pyridines, and heavy metal complexes are represented among these active compounds. Sulfonamides were both the most potent (BL22910, SD_{50} = 39.5 mg/kg, G.I. = 1.5) and least potent (BL22876, SD_{50} = 155 mg/kg, G.I. = 3.48) of the active compounds.

AJ07615, a diaminopyrazine, was the only active compound among approximately 250 pyrazine or quinazoline inhibitors of dihydrofolate reductase tested. Compounds of these classes and biologic activity are an expressed interest of the World Health Organization Steering Committee on the Chemotherapy of Leishmaniasis. In our system the compounds showed little activity and were frequently toxic.

Constituting a part of the total 1,684 compounds, a group of 44 antiviral compounds were studied. The majority of these compounds were both

inactive and not toxic at dosage levels of 52, 208, and 416 total mg/kg administered intramuscularly. Only three of these compounds, BL31197, BL31099, and BL31508 had possible antileishmanial activity, being 48%, 34%, and 32% suppressive respectively at 416 total mg/kg.

Detailed results for all active and inactive compounds are on file in computer data bases at the Division of Experimental Therapeutics, WRAIR.

2. Glucantime Reference Data

The reference compound, Glucantime, is included in each experiment routinely at three dosage levels. These dosage levels are based on an assay of antimony content. The SD_{50} is calculated for the reference compound in each experiment and is used for comparison of the efficacy of any active compounds in that experiment. To provide some indication of the variation of the reference data, for three consecutive years of this contract the mean and standard deviation for the SD_{50} values for Glucantime from 23, 37, and 30 experiments conducted during these report periods respectively were calculated. The data from individual experiments is summarized in Appendix 1, Table III. The mean SD_{50} for Glucantime was calculated to be 71.2 mg/kg (SD $\pm$ 27.5),54.3 mg/kg (SD $\pm$ 25.6) and 60.8 mg/kg (SD $\pm$ 36.4).

Dosage levels of 26, 52, and 208 mg/kg were used for all experiments in order to estimate as accurately as possible the SD_{50} and avoid the artifactual variations in the dose response curve and inflated SD_{50} that had been noted when higher doses had been used. Natural variation in response to the drug, particularly at the lowest dose, still results in some degree of variation of the SD_{50}. This points to the importance of including the reference compound in each experiment rather than using a historical mean value for the reference compound to compare the efficacy of test compounds.

3. Special Cooperative Studies

A total of 26 compounds was selected for these _in vivo_ studies based on known previous _in vitro_ activity, previous evidence of _in vivo_ activity, or suspected of having _in vivo_ activity because of several other types of evidence. These studies included a comparison of the _in vivo_ activity of Glucantime, amphotericin B, pentamidine, ketaconazole, a number of purine analogs, as well as a variety of other compounds against visceral leishmaniases in the hamster when administered _via_ various routes. Glucantime Indexes (G) were calculated for 15 of these compounds and the relative activity of the others were ascertained with some accuracy. The antifungal agent, amphotericin B when administered intravenously was the most active of this group of compounds (G = 27.33). This compound was less active when administered _via_ the intraperitoneal route (G = 2.54). The purine analog, formycin B, administered orally was was the second most active of the compounds studied in this experiment(G = 3.13). When administered _via_ the intramuscular route, the activity was lower (G = 1.36). Formycin A administered _per os_ (G = 1.88) and pentamidine administered intramuscularly (G=1.02) were the next in the order of descending activity. The next most active compounds were 3-deazaguanosine and 9-deazainosine with Glucantime Indexes of 0.38 and 0.36 respectively when administered orally. The other compounds studied including allopurinol had activity less than those mentioned above.

Of the purine analogs studied, the only one for which greater than 95% suppressive dosage did not result in toxicity was 9-deazainosine.

4. Liposome Studies in Hamsters

A comparison of the antileishmanial activity of liposome-encapsulated Glucantime, pentostam, formycin B, and amphotericin B with that of unencapsulated Glucantime, pentostam, formycin B, and amphotericin B was done

in hamsters infected with <u>Leishmania donovani</u>. Liposome-encapsulation generally resulted in enhanced antilesihmanial activity against amastigotes in both the spleen and liver. Liposome-encapsulated Glucantime was 800-900 times as active as the unencapsulated drug (Berman et al., 27) and liposome encapsulated amphotericin B was 2-5 times as active as unencapsulated amphotericin B (Berman et al., 27). Furthermore, liposome-encapsulated amphotericin B was 300-700 times more active than unencapsulated Glucantime. Therapeutically effective dosages of liposome-encapsulated amphotericin B were not toxic.

5. Efficacy of WR06026

A. Analogs

The structures of WR06026 analogs studied during the contract period are shown in Appendix 2, Figure 2. These analogs are all prodrugs which would be expected to be converted to the major hydroxy metabolite of WR06026 by the host. Since route of administration might significantly affect metabolism of these compounds, their efficacy against <u>Leishmania donovani</u> infection was determined after oral, intramuscular, or intracardial administration. In some cases, spleen parasite burdens were determined in order to ascertain the efficacy of the compounds at infection sites other than the liver, the primary site of metabolism.

The antileishmanial activity of the analogs in the liver was not as great as that of WR06026 regardless of the treatment regimen, dosages, or route of administration used.

Based upon suppression of parasite burdens in the spleen, however, WR06026 was significantly more effective, particularly at lower dose levels, against extrahepatic infection when administered orally. Similarly, all analogs except BL52749 were more efficacious at suppressing liver parasite burdens when administered orally. Oral administration of the analogs had a highly variable effect upon spleen parasite burdens. Significant variations in numbers of parasites in the spleen among individual animals within treatment groups resulted in the somewhat capricious nature of the spleen data. Neither WR06026 nor the analogs were toxic at dosage levels used in these studies.

B. Efficacy of WR06026 when Administered Prior to Infection

As can be seen from Appendix 1, Table IV, WR06026 is 90% suppressive when administered <u>per os</u> as a single treatment of 10 mg/kg three days prior to infection. A single treatment of 0.1 mg/kg given on days 3, 2, or 1 prior to infection was up to 65% suppressive. While 0.1 mg/kg was active when administered on days 3 and 2 or days 3, 2, and 1 prior to infection, this activity was similar to that obtained with a single treatment.

WR06026 was also highly effective when administered in a sir[illegible] oral dose 3 days prior to infection (Appendix 1, Table V, Group I), but [illegible]s not as effective as when administered 3 days after infection (Group II), [illegible]ecially at lower dose levels. An additional group was included in the expe[illegible]ent (Group III) in order to compare results from groups of animals treat[illegible] preinfection, all of which were necropsied 10 days after drug adminis[illegible]ation. Again, postinfection administration of the drug was somewhat more eff[illegible]ive than preinfection administration, and the delay in necropsy had virtua[illegible]ly no effect on suppression of parasite burden in comparison to Group II an[illegible]als which were necropsied 3 days sooner.

WR06026 analogs were quite active in suppressing numbers of hepatic parasites at the single dose level tested when administered postinfection. This activity dropped significantly when the analogs were administered preinfection (Table VI). In the spleen the analogs were, like the parent

compound, much less active than in the liver when administered postinfection, but little difference between pre- and postinfection treatment was seen in suppression of numbers of parasites in the spleen by any of the analogs, with the possible exception of BL34296. In three instances (BL52196, BL52749, BL53308) suppressive activity was apparently greater in the spleen than in the liver when the compounds were administered prior to infection.

A followup experiment was performed to determine if suppression of parasite numbers in the spleen could be enhanced if a larger dose of WR06026 was administered. The experiment was performed exactly as the previous one, but only WR06026 was used and the highest dose level was increased to 6.5 mg/kg administered as a single oral dose. Increased drug doses resulted in greater suppressive activity in the liver when animals were treated preinfection and in the spleen when animals were treated postinfection; however, even a four-fold increase in the amount of drug administered failed to significantly increase its suppressive activity in spleens of animals treated prior to infection.

6. Optimization Study of Selected 8-aminoquinolines

The effect of route of administration on efficacy against *Leishmania donovani* for six 8-aminoquinolines is summarized in Appendix 1, Table VII and their structure shown in Appendix 2, Figure 3. All compounds were very active and virtually abolished infection when administered either intrasmuscularly or orally at 3.25 mg/kg total dose. With the possible exception of AP45845, no significant differences in suppressive activity was observed between the two routes of administration at any dose level.

7. Comparison of the Efficacy of Selected Compounds Against *L. donovani*

When compared in a single experiment, the antileishmanial efficacies based on SD_{50}'s of amphotericin B, Glucantime, 9-deazainosine, pentamidine, sinefungin, and WR06026 were observed to be WR06026 > sinefungin > amphotericin B > Glucantime > 9-deazainosine > pentamidine. When studied at dosage levels resulting in parasite suppression approaching 90-100%, sinefungin was toxic as indicated by roughened hair coat of the treated hamsters, and amphotericin B and pentamidine were toxic as indicated by weight loss and/or mortality in treated hamsters.

8. Combination Studies

Results from the study to determine the effects of combined treatment with sinefungin (WR254847) and each of 6 purine analogs previously found to be active in our system are summarized in Table VIII. No antiparasitic activity significantly greater than that attributable to sinefungin alone was observed when animals were treated with both sinefungin and any one of the purine analogs.

9. Studies with Derivatives of Berberine

The activities of these compounds in the primary visceral test system are summarized in Table IX and discussed in detail by Vennerstrom, *et al.* (28). Structures for these compounds can be found in Appendix 2, Figure 4. Only 8-cyanodihydroberberine at a total dose of 208 mg/kg and tetrahydroberberine and N-methyltetrahydroberberinium iodide, both at 416 mg/kg suppressed parasite numbers by 50% or more. Among these compounds, 8-cyanodihydroberberine appeared to be the most toxic as evidenced by a loss of 18% total group body weight; however, the 11% weight loss in the group treated with N-methyltetrahydroberberinium iodide suggests that this compound may be more toxic than the equally antiparasitic tetrahydroberberine. None of the compounds showed 50% suppressive activity at 52 mg/kg. In contrast, the reference compound, Glucantime, suppressed parasite numbers by 72% at this

dose level. Therefore, tetrahydroberberine, the most potent and least toxic of the compounds was found to be less effective than Glucantime against *L. donovani*.

In regard to structure-activity relationships, the best activity at 416 mg/kg was seen with tetrahydroberberine and N-methyletrahydroberberinium iodide, both of which have a tetrahydroberberine skeleton. The weight loss associated with the quaternary N-methyltetrahydroberinium iodide suggests that this compound is more toxic than the almost equally active tetrahydroberberine. It would thus appear that further investigation of tetrahydroberberine derivatives without a quaternary nitrogen for treatment of visceral leishmaniasis is warranted. The activity of 8-cyanodihydroberberine may have resulted in part from its oxidation to the corresponding quaternary structure; an analogous oxidation has been reported (Devi, 29) for dihydroberberine. Surprisingly, however, palmatine chloride, a quaternary derivative which differs from berberine only in the substitution of a methylenedioxy for a bis-methoxy at the 2,3 position, was inactive.

It would therefore appear that a quaternary nitrogen was associated with antileishmanial activity in this test system, but was also associated with toxicity. The latter observation may be an artifact of the system. The treatment of hamsters infected with *L. donovani* at a time when the animals were undergoing a period of rapid growth possibly made them more sensitive to treatment associated weight loss or inhibition of growth. Therefore, conclusions regarding the toxicity of the test compounds based upon weight loss alone cannot be considered absolute, but this parameter is a useful indicator of relative toxicity of compounds within the same test system.

B. *In Vivo* Studies Using the Monkey Model

1. Liposome Study in Monkeys

The results of this experiment have been presented by Berman et al., (27). Unencapsulated Glucantime, the reference compound, when administered at a dosage level of 104 mg/kg/day (MKD) administered on days 17-23 after infection eliminated greater than 98% of the amastigotes of *L. donovani* in the spleen, liver, and bone marrow of infected monkeys but caused the death of 1 of 3 of the experimental monkeys. Unencapsulated amphotericin B administered at 2 MKD on days 17, 20 and 23 eliminated more than 95% of the parasites in the spleen and liver and greater than 50% of the amastigotes in the bone marrow but both monkeys receiving this dosage level died due to toxicity of the compound. Liposome encapsulated amphotericin B administered at a dosage of 2 MKD on days 17, 20, and 23 eliminated 90-95% of the amastigotes in the spleen and liver and approximately 69% of the parasites in the bone marrow without causing any deaths of the monkeys. When the dosage of liposome encapsulated amphotericin B was increased to 4 MKD on days 17, 20, and 23 greater than 98% of the parasites were eliminated but 1 of 3 monkeys died. A single treatment on day 17 with 4 MKD of liposome encapsulated amphotericin B did not cause the death of any monkey but eliminated only 71-90% of the amastigotes in the spleen and liver respectively and approximately 69% of the amastigotes in the bone marrow.

Empty liposomes appeared to have some suppressive effect. Additional studies will be necessary to verify this observation.

Hematologic and microscopic pathologic studies revealed no difference between the treated and untreated groups.

2. WR06026 Study in Monkeys

WR06026 was highly suppressive in the livers of all monkeys receiving total dosage levels of 120, 60, or 15 mg/kg body wt. (100%, >99%, and 91% respectively). No parasite suppression was seen in monkeys receiving total

dosages of 3.75 or 0.94 mg/kg. Parasites in the spleens of monkeys receiving a total dosage of 60 mg/kg of WR06026 were highly suppressed (100%) while parasites in spleens of those receiving a total of 15 mg/kg were approximately 50% suppressed. It is of some interest to note that the absence of the spleen had no apparent effect on the efficacy of WR06026 as determined from parasite numbers in the liver and bone marrow.

Numbers of amastigotes in the bone marrow of treated monkeys were not suppressed at any drug dosage level used. WR06026 was not suppressive in any organ studied at total dosages of 3.75 or 0.94 mg/kg.

3. 9-deazainosine Study in Monkeys

9-deazainosine was highly active in the spleen, liver, and bone marrow at a total dosage of 1400 and 350 mg/kg. Dosage levels of 200 or 50 MKD of this compound administered for seven days eliminated 99% of the amastigotes in the liver and 96% of the parasites in the spleen. The activity of the lower dosage of 9-deazainosine was approximately equivalent to 52-104 MKD of the reference compound, Glucantime. No weight loss was noted in any of the groups of monkeys. Details of these studies are presented by Berman et al., (30).

Hematology studies based on a complete blood count revealed no significant differences between the vehicle control group and those receiving 9-deazainosine. Based on the histopathology studies of selected major organs only two major differences was observed between the group receiving vehicle only and the group receiving the highest dosage level of 9-deazainosine. Fatty livers were noted in all three monkeys receiving the high level of 9-deazainosine while only one of three receiving vehicle had any evidence of fatty change. Numerous granulomas were observed in the livers of the vehicle control group while granulomas were sparse in those monkeys receiving the high level of 9-deazainosine. Numerous amastigotes were observed in the granulomas of vehicle controls while the granulomas in those receiving 9-deazainosine contained very few amastigotes.

We interpret the fatty change in the livers of the 9-deazainosine treated group as indicative of drug toxicity.

C. *In Vitro* Studies

Although the basic procedure for the mouse macrophage test system described by Neal and Croft (23) was used, experiments were carried out to establish in this laboratory the number of macrophages per well to be used, the ratio of amastigotes to macrophage to be used with the WR378 strain of *Leishmania*, and to determine the amounts of the reference compound, Glucantime, which would result in parasite suppression of approximately 90%, 50%, and 30%.

While at this point the data remains preliminary and the results presented here are somewhat subjective, it appears that 2×10^5 macrophages per well derived from CD_1 mice will be the ideal number. Trials in which the ratio of amastigotes to macrophages was 3, 2, or 1 resulted in destruction of the macrophages by the parasites by day 12 indicating that the ratio used by Neal and Croft (23) with another strain of *Leishmania* would require modification in this laboratory. Similar results were obtained when the promastigote stage of the parasite was used. Conflicting data resulted when infected wells were treated with comparable dosage levels of Glucantime.

II. Studies Involving Leishmania braziliensis panamensis Using the Hamster Model

A. Confirmation of Validity of Cutaneous Test System

Following intracutaneous inoculation of hamsters near the base of the tail with 1.5×10^7 promastigotes of Leishmania braziliensis panamensis, cutaneous lesions increased in size generally 1-6 weeks reaching a maximum mean area of approximately 112 mm^2 by 6-8 weeks after infection and the area generally remained approximately the same for the next 8-10 weeks. Approximately 14-16 weeks after infection, lesions on some hamsters were observed to decrease in size, and during the next 12-15 weeks lesions on most hamsters decreased in size leaving subcutaneous granulomas. Lesions persisted indefinitely on some hamsters. The weight of the lesion correlated closely with the area of the lesion.

Quantitation of the amastigotes in lesions from hamsters killed at weekly intervals after infection revealed that the mean total numbers of amastigotes per lesion increased during the first three weeks with maximum mean numbers of approximately 3.5×10^7 observed at three weeks. A gradual decrease in numbers occurred during the next four weeks after which the mean numbers of amastigotes per lesion decreased sharply and by 14 weeks after infection the mean number per lesion had decreased to approximately 9.5×10^5. The numbers of amastigotes remained low subsequently.

Following treatment of hamsters with 416, 208 or 52 MKD of Glucantime on days 19-22 after infection the lesion size decreased approximately 89%, 82% and 51% respectively when measured one week after completion of treatment. When measured 7 weeks after completion of treatment, the lesion suppression at these dosage levels was approximately 67%, 67% and 24% respectively. The numbers of amastigotes in lesions of hamsters treated with 416, 208, or 52 MKD Glucantime on days 19-22 were decreased approximately 99%, 99%, and 97% respectively when counted one week after completion of treatment and were decreased approximately 99%, 94%, and % when counted 7 weeks after completion of treatment.

A reasonably close correlation existed between lesion size and numbers of amastigotes during the first six to nine weeks after infection in the untreated hamster. In addition, following drug therapy on days 19-22 after infection, lesion size and numbers of amastigotes decreased concomitantly when quantitated at one or seven weeks after treatment. Thus suppression of lesion size is an excellent indicator of the suppressive effects of antileishmanial drugs on the numbers of amastigotes in the lesions during the first six to nine weeks after infection.

B. Glucantime Reference Data

The reference compound, Glucantime, is included in each experiment routinely at two dosage levels. These dosage levels are based on antimony content of the compound. The SD_{50} is calculated for the reference compound in each experiment and is used for comparison of the efficacy of any active compounds in that experiment. To provide some indication of the variation in the data obtained, the mean and standard deviation for the SD_{50} values r three experiments conducted during this project period were determined (Table X). The mean SD_{50} was calculated to be 159.3 $\pm$ SD 20.6. The SD_{50} for Glucantime in this system is approximately 2-fold greater than for the visceral test system probably due to differences in drug distribution between skin and liver.

C. Primary Cutaneous Test System

A total of 410 compounds were studied for suppressive activity against *L. braziliensis panamensis*. Forty-one (Table XI) of these were active (greater than 50% lesion suppression). Glucantime Indexes were calculated for five of these 41 active compounds. Sinefungin (Glucantime Index ranged from 12.7 to 30.2) and WR06026 (Glucantime Index = 15.7) were the most active. Two compounds (AR80315 and ZP43609) were less active than Glucantime (Glucantime Index = .379 and .857 respectively) while the activity of the remaining compound, AJ15304 was approximately equal to that of Glucantime (Glucantime Index = 2.58).

Ninety of the 410 compounds tested were found to be toxic as indicated by death of hamsters and/or greater than 15% loss of weight. A list of inactive compounds for this screen can be found in Table XII.

D. Special Cooperative Studies

Amphotericin B was only marginally active against *L. b. panamensis* when administered intravenously at the highest dosage used (3.25 mg/kg body weight in a single injection). Formycin B, total dosage of 160 mg/kg body wt., was significantly active (61% suppression) when administered intramuscularly but was toxic at this dosage level. This compound was not active when administered orally and amphotericin B was not active when administered *via* the intraperitoneal route.

Allopurinol and formycin A were not significantly active when administered *via* either the oral or intramuscular routes. Allopurinol was toxic at 1664 total mg/kg when given intramuscularly. All hamsters receiving 1040 total mg/kg of formycin A orally died before completion of the experiment while significant toxicity was noted in hamsters receiving 52 total mg/kg of this compound *via* the intramuscular route.

E. Studies with Derivatives of Berberine

The quaternary alkaloid berberine and several of its derivatives (Figure 3) were tested for efficacy against *L. braziliensis panamensis*. Several of these compounds were noted to have some suppressive activity.

Data in Table XIII show the percent suppression of lesion area in hamsters infected with *L. braziliensis panamensis*. At the indicated doses all of the compounds tested were relatively nontoxic, and with the exception of berberine itself, appeared to be less effective (structures 2, 4, 7, 8, 9) or equipotent (structures 3, 5, 6) in the cutaneous test system as in the visceral test system. The two most active compounds, berberine and 8-cyanodihydroberberine, produced 56% and 46% suppression of lesion area respectively when administered at a total dose of 208 mg/kg. In comparison Glucantime suppressed lesion development by 66% at this dose. These data suggest that berberine and 8-cyanodihydroberberine are approximately as effective as Glucantime against *L. braziliensis panamensis* in our model.

III. Studies Performed During the Extension Period Involving *Leishmania donovani*

A. Primary Screen

Seventeen compounds were studied for suppressive activity against *L. donovani* during this period. Eleven of these were tested at two drug dosage levels (208 and 52 mg/kg total) while six were studied at three dosage levels (416, 208, or 52 mg/kg total). None of the 17 compounds were active (Table XIV) and three of these were toxic as indicated by the death of hamsters.

B. Combination Studies

1. Oxyformycin B and Sinefungin

The results of this experiment are summarized in Table XV. No significant enhancement of parasite suppression was noted in hamsters receiving both oxyformycin B and sinefungin when compared to those hamsters receiving sinefungin alone. These compounds were not toxic when administered alone or in combination.

2. Paromomycin, Neomycin, and Gentamycin Sulfate

Neither paromomycin, neomycin, nor gentamycin sulfate were active (greater than 50% parasite suppression) when administered intraperitoneally alone or in combination against three day infections of L. donovani (Table XVI). No toxicity (death or 15% or greater loss of weight) was noted in hamsters receiving these compounds alone or in combination.

3. Liposomal Muramyl Tripeptide (MTP) and Glucantime

Liposomal MTP alone showed no efficacy against the parasite; in fact it appeared that the infection was enhanced in animals receiving either dose of MTP alone (Appendix 1, Table XVII). A combination of Glucantime and MTP showed little improvement over the efficacy of Glucantime alone, except when both Glucantime and MTP were used at the maximum doses tested (208 mg/kg and 400 μg tested respectively).

Untoward behavior and appearance among some groups early in this experiment led to the request of a veterinary pathologist to record gross observations on animal appearance within the first 24 hours after the initial injection of MTP. The most commonly appearing gross pathologic observations described from hamsters given MTP were weight loss, torticollis, discharge from the eyes, photophobia, and difficulity in walking. The details of the gross pathologic observations can be seen in Appendix 3. The pathologist was unaware of the nature of the treatment at the time the observations were made. The apparent toxicity attributable to MTP would seem to far outweigh any antiparasitic advantage afforded by the combination therapy.

C. Optimizing Regimen for Sinefungin

As summarized in Table XVIII (Appendix 1) no detectable difference was noted in parasite suppression in hamsters receiving a total dosage of sinefungin at 52 or 6.5 mg/kg in one, two, four, or eight treatments. Notable differences were apparent however in hamsters receiving a total dosage of sinefungin at 3.25 mg/kg in that parasite suppression was enhanced concurrently as the number of treatments were increased.

DATA PROCESSING

During this contract in collaboration with officials at WRAIR, a new system for processing data was written, installed, revised and verified for both the L. donovani and L. braziliensis test systems. A new IBM-PC XT microcomputer was purchased with a DOS operating system which was compatible with WRAIR's VAX and the IBM-PC used by the COTR. There were several advantages of this new system over the old one which operated on CPM.

Since the IBM computer had a maximum record length of 220 bytes (twice that of the Televideo previously used) all pertinent data on a given test compound in any one experiment could be compiled into one record (line). This pertinent information contains bottle number, experiment number, drug route, drug regimen, test system, animal species used, parasite species used, julian date of infection, dosage levels used, percent weight change at each dosage level, number of amastigotes (or lesion size) of each animals for each dosage, parasite suppression of each dosage level, standard deviation, and Glucantime Index.

The ability to compile this information into one record permitted the establishment of a database which enables the retrieval of any desired information on a given compound in a matter of minutes and display the data to the viewer. In collaboration with the Department of Experimental Therapeutics, WRAIR, during the last fifteen years, the world's largest data base on the experimental chemotherapy of leishmaniasis has been generated (approximately 7,000 compounds in the L. donovani system alone representing over 1 million bytes of data). Quick retrieval of the data was advantageous for WRAIR, the COTR, and this laboratory. Data could also be sorted using this system by date, bottle number, percent suppression, or Glucantime Index. Several tables used in this report (i.e. Tables I, II, III, X, XI, XII, and XIV) were generated in this way.

Another advantage of this new computer was the increased memory capability (512 KB as compared to 64KB of the Televideo). This expanded memory allowed for the storage of the large data base of test systems generated over the last 16 years and provided additional memory for the constant updating of newly acquired data.

The new programs written for this system by Major Patrick McGreevy, WRAIR, analyzes the data using linear and non-linear regression. Glucantime Indexes are calculated using SD_{50} values rather than the SD_{90} values used with the Televideo system. By lowering the SD value, additional promising compounds were brought to the attention of the COTR in the form of Glucantime Indexes.

DISCUSSION

The potential threat of the leishmaniases to the health of military and other personnel operating in many areas of the world (Kinnamon et al., 1; Mahmoud and Warren, 5; Takafuji et al., 12; Chance, 31) is significant. Chemotherapy is the only practical method of treatment for these parasites. Selection of a suitable drug for the treatment of the leishmaniases is difficult. While the pentavalent antimonials are generally effective, and, as careful recent studies have shown, probably are less toxic than previously believed, (Bryceson, 14), they are not always curative, due to a variety of reasons including the possibility that some strains of Leishmania have some degree of antimony resistance. Other liabilities associated with the antimonials are that they must be administered parenterally, and often repeated injections are required. Thus it is believed by many that the development of highly active but potentially less toxic drugs is warranted especially for use in cases of visceral leishmaniasis and certain cutaneous strains which are not cured by current antimony therapy. The development of new drugs for use against the leishmaniasis historically has been difficult and this difficulty is indicated by the fact that no new drug has been introduced for general use against this group of diseases in more than 40 years (Neal, 13). This project as well as previous work in this laboratory has been devoted to the development of better chemotherapeutic drugs for the treatment of these parasites.

Because of differences in the various strains of Leishmania and especially because of the different sites of infection with these parasites, probably no single drug will be appropriate for the treatment of all. Thus we developed a combination of test systems which would address all of these issues during the testing of potential antileishmanial drugs. The primary visceral test system dealt with issues pertinent to the visceral species of Leishmania and the primary cutaneous test system dealt with issues relevant to the cutaneous species of Leishmania. Antimony resistant strains of both visceral and cutaneous species were developed and were available in this laboratory for use in testing promising new drugs and this part of our test system was designed to deal with the question of identifying new drugs for the treatment of drug resistant Leishmania.

In the pursuit of our objectives to develop new improved chemotherapeutic drugs for Leishmania, we were cognizant that due to the relatively benign nature of cutaneous leishmaniasis in U. S. soldiers, any new drug for general use ideally should be highly efficacious, non-toxic, and preferably administered orally.

During the course of this and previous contracts, 8-aminoquinolines have proven to be the most consistently active compounds against Leishmania donovani of any class of compounds tested. The antileishmanial activity of one 8-aminoquinoline, the lepidine WR06026, was discovered early in the course of an initial USAMRDC contract held by this laboratory (Kinnamon et al., 32) and is now in the early stages of clinical testing. Primary screening of other 8-aminoquinolines continued during the current contract principally because of the possibility of discovery of even more potent and less toxic compounds of this class that might serve as alternatives to WR06026 should the latter compound demonstrate less than desirable clinical activity during the course of its development. This potentiality was especially important in regard to the lack of consistent evidence in animal models for efficacy of WR06026 against New World cutaneous leishmaniasis. In view of the equivocal results that have been obtained in previous years with WR06026 in our cutaneous system, it was important to discover compounds of this class that have activity against visceral leishmaniasis approximating that of WR06026, while demonstrating more consistent efficacy against cutaneous infection. Continued emphasis has been placed upon discovery of compounds of this class that are equally or more effective administered orally or parenterally as was the case with the 8-aminoquinolines of this type investigated during this contract.

Continued experimental interest in WR06026 centered upon this drug's metabolism, in particular the duration of its metabolites' antiparasitic activity and their distribution to infected tissues other than the liver. In the experiments performed during this contract period, studies showing that administration of WR06026 three days prior to infection resulted in significant parasite suppression. This observation strongly suggested that the active metabolites of this compound are long-lived. This is in contrast to physio-chemical data showing that the metabolites thus far identified can be detected in the host body fluids for less than 24 hours. It was more clearly demonstrated during this contract period that the suppressive activity of WR06026 in extrahepatic infection sites such as the spleen is dose dependent. It would appear that significantly higher drug doses are required to clear parasites from the spleen and by extension the bone marrow than from the liver. This observation could be significant for the eventual clinical use of WR06026. Additional studies resulting from our initial observations that the active metabolites(s) of WR06026 have a more extended life than that of previously identified and characterized metabolites and that no single known metabolite is alone as potent as the parent compound were confirmed by our most recent studies (Hanson et al., 33). Furthermore, in animals treated 3 days prior to infection, it was observed that the active metabolites(s) is not only relatively long-lived, but that it is able to be delivered to extrahepatic sites for at least 3 days after administration. In contrast to animals treated post infection, no dose dependent suppression in the spleen was observed in pretreated animals, even at higher drug doses.

Despite the amount of pharmacologic and parasitologic work that has been devoted to the study of the metabolism of WR06026, many questions remain. The performance of this drug in clinical trials will help to answer some of these questions. It is anticipated, however, that clinical trials will generate further questions regarding the bioavailablity and metabolism of this compound, and these questions will continue to be addressed initially in the hamster model.

Because <u>Leishmania</u> cannot synthesize purines <u>de novo</u>, but must rely on salvage pathways, purine analogs have received a good deal of attention as possible antileishmanial agents, including work done in this laboratory (Berman, et al., 30; Hanson, et al., 33). A study of the <u>in vivo</u> activity of several purine analogs gave a ranking of activity of allopurinol < 9-deazainosine < formycin A which is comparable to formycin B. The ranking of activity recorded for these compounds <u>in vivo</u> in the hamster model is similar to that obtained by Berman (unpublished observations as stated in reference 30) against <u>L</u>. <u>major</u> <u>in vitro</u> in human monocyte-derived macrophages. Since these two models have obtained similar data on the antileishmanial activity of this group of compounds using two different species of <u>Leishmania</u>, one <u>in vivo</u> and the other <u>in vitro</u>, Berman <u>et al</u>. (30) have suggested that the activity of the purines can be assessed appropriately with these two models.

Followup studies of 9-deazainosine in squirrel monkeys showed that this compound was at least as active and probably more active in the monkey than Glucantime which is currently used in the treatment of visceral leishmaniasis in human beings. There was some suggestion that 9-deazainosine may have some toxic effects on the liver of the squirrel monkey. One advantage of 9-deazainosine over Glucantime is that the former can be administered orally whereas the latter must be administered parenterally. Berman et al. (20) have suggested that consideration should be given to the development of 9-deazainosine as an oral treatment for human visceral leishmaniasis. The potential of this compound for use against antimony resistant <u>Leishmania</u> should also be considered.

Synergism between some of these purine analogs and sinefungin against <u>L</u>. <u>donovani</u> promastigotes <u>in vitro</u> has been reported (Nolan, 4). In our visceral test system, neither synergy nor an additive effect was observed between sinefungin and any one of the purine analogs tested.

The marked enhancement of the antileishmanial activity of Glucantime by encapsulation into liposomes previously reported (Alving et al., 35) raised the question of whether the activity of other compounds could also be enhanced by this technique. Of considerable importance are the observations in these studies that liposome encapsulated amphotericin B is highly active with low toxicity against L. donovani in both hamsters and squirrel monkeys. Unencapsulated amphotericin B is also active but therapeutic dosages may be toxic. However therapeutic dosages of liposome encapsulated amphotericin B equivalent to those used in these studies which are highly efficacious against L. donovani in hamsters and monkeys have been shown previously not to be toxic to the kidneys or other organs in human beings (Berman et al., 27). Liposome encapsulated amphotericin B is 60 times more active in the squirrel monkey than unencapsulated Sb (Glucantime). Berman et al. (27) have suggested that the demonstration of high rodent and monkey efficacy with a clinical formulation of liposome encapsulated amphotericin B suggests that it should be considered for clinical trials in humans suffering from visceral leishmaniasis. One drawback associated with liposome encapsulated drugs is that in our experience, some toxicity is associated with administration of liposomes. These observations coupled with the difficulty of obtaining stable liposome preparation detracts considerably from their potential use in human beings.

The relationship between lesion area and density of amastigotes in cutaneous leishmaniasis as documented here is, to our knowledge, the first information of this type available. Several significant points regarding these studies would appear to warrant further discussion. First, the observation that lesion area and numbers of amastigotes increase concomitantly during the early stages of the infection (1-3 weeks after infection), remain relatively constant for the next 4 weeks, and subsequently the numbers of amastigotes decrease sharply while lesion area generally remains unchanged has some practical implications. For example, in culturing lesions for the presence of parasites as a part of routine diagnostic procedures, the data suggest that older lesions may yield fewer positive cultures. Second, the observations that following chemotherapy during the early stages of the infection (days 19-22 after infection) the lesion area and the number of amastigotes are suppressed concomitantly verifies that evaluation of lesion area represents a valid assessment of the antileishmanial activity of the drug. Thus the primary cutaneous test system used in this laboratory for the assessment of the antileishmanial activity of test compounds is sound.

Although several hundred compounds were studied during this project period for activity against L. b. panamensis, very few of were active. Some of the cutaneous leishmaniases are especially difficult to treat (Neal, 13). For example, a comparison of the mean SD_{50} values of Glucantime obtained during the project period between L. donovani and L. b. panamensis shows that the SD_{50} for the latter is approximately two-fold greater than that for the former. This difficulty in therapy is reflected in the results obtained in our studies of the compounds for activity against L. b. panamensis during this contract as well as previous years. Limited success has been achieved in identifying compounds which are active against this parasite in hamsters. Generally compounds found active against L. donovani are not active against L. b. panamensis. Undoubtedly location in the skin and thus the difficulty of getting adequately high therapeutic concentrations of drugs to this location contribute to the difficulty in treating the cutaneous species. Numerous other factors also are undoubtedly involved.

There have been several reports regarding the experimental and clinical efficacy of berberine against both visceral (DasGupta and Dikshit, 36; Ghosh, et al., 37; Ghost, et al., 38) and cutaneous leishmaniasis (Das Gupta and Dikshit, 38; Devi, 29; Karamchandani, 39; Varma, 40); however, information regarding antileishmanial activities of berberine derivatives has been anecdotal (Putzer, 41). The synthesis of several berberine derivatives by the Department of Medicinal Chemistry, WRAIR, provided an opportunity to test

these alkaloids in controlled experiments for antileishmanial efficacy in visceral and cutaneous leishmaniasis. Although several of these derivatives showed activity against either Leishmania donovani or Leishmania braziliensis panamensis or both, their activities and toxicities relative to the reference compound, Glucantime, are not presently encouraging as to their potential widespread clinical utility. Several interesting problems do, however, remain, e.g. clarification of the contribution of a quaternary nitrogen to the activity and/or toxicity of the compounds and the potential for local administration of the compounds in cases of cutaneous leishmaniasis due to nondisseminating Old World species.

During the six-month technical extension period of this contract, the study of an additional 17 compounds in the primary screen for antileishmanial activity completed the testing of those compounds selected for study during this contract period.

In vitro studies performed by Dr. Linda Nolan at the University of Massachusetts under USAMR&D command, contract number DAMD17-81-C-1198, indicated that combinations of certain purine analogs with sinefungin resulted in enhanced antileishmanial activity. In the present studies, oxyformycin B which was one of the more active of the purine analogs studied by Dr. Nolan, was studied in combination with sinefungin for activity against L. donovani in hamsters. In contrast to the results obtained in the in vitro studies, no synergistic antileishmanial activity was noted in hamsters with this combination. The reasons for this difference are not known at this time.

Paromomycin in combination with other drugs is used currently as a topical therapy for cutaneous leishmaniasis in certain parts of the world (El-on et al., 42, 43). Since an alternative preparation is being studied at WRAIR, it became of interest to determine the antileishmanial activity against L. donovani in hamsters of paromomycin in combination with antibiotics that would be included in this new topical preparation. Paromomycin had been shown to have activity against L. donovani in hamsters when administered via the intramuscular route. The antileishmanial activity of paromomycin in this experiment was less than observed in the previous experiment. This difference may possibly be attributed to the administration of paromomycin via the intraperitoneal route rather than the intramuscular route as in the previous experiment. The intraperitoneal route was chosen in this experiment to standardize the route for both the antibiotic and paromomycin. Combination studies including paromomycin and antibiotics will require further study and such studies will be carried out during the new contract (DAMD17-90-C-0131).

The relative importance of the roles of host immune response and direct effect of drug activity in the in vivo killing of Leishmania has been of considerable interest (Hanson, 44; Adinolfi et al., 45). Some evidence is available suggesting that immunopotentiating agents such as muramyl dipeptide (MDP) enhances the antileishmanial activity of Glucantime which is one of the standard drugs currently used in the treatment of leishmania in human beings (Adinolfi et al., 45). The present studies were undertaken to determine if a different adjuvant, muramyl tripeptide (MTP, Ciba Geigy Corp., Summit, N. J.), might enhance the antileishmanial activity of Glucantime. In contrast to the observation of others with MDP (Adinolfi et al., 45), MTP had no enhancing effect on the antileishmanial activity of Glucantime in hamsters against L. donovani. MTP was toxic to hamsters in our experiment at dosage levels considerably lower (200 μg/kg total dosage) than those of MDP (1200 μg/kg) used by Adinolfi et al (45).

Since sinefungin was one of the more active compounds studied during this contract against L. donovani, it was of considerable importance to determine the most efficacious dosage regimen. Varying the dosage regimen had little or no effect on the efficacy of this compound at higher dosage levels (52 mg/kg total dosage), but the efficacy increased with the number of treatments at lower dosage levels (3.25 mg/kg total dosage).

CONCLUSIONS

1. The 8-aminoquinolines were the most active antileishmanial compounds studied for efficacy against Leishmania donovani. The 8-aminoquinoline, WR06026, and its analogs were highly efficacious in suppressing numbers of hepatic amastigotes but were less active against splenic parasites when administered as a single dose 3 days after infection. When administered prior to infection, the activity in the liver and spleen was approximately equal.

Increase in dosage levels of WR06026 resulted in greater suppressive activity in the liver when treatment preceded infection and in the spleen when treatment was administered subsequent to infection.

The efficacy of the 8-aminoquinolines was approximately equal against Leishmania donovani when administered orally or via the intramuscular route.

2. Purine analogs had relatively low efficacy against Leishmania and often the large quantity of compound required to eliminate the parasites was toxic to the host.

3. As a group, the pyrazine or quinazoline inhibitors of dihydrofolate reductase did not appear to be a promising candidate for antileishmanial drugs since these compounds generally had little antileishmanial activity and were often toxic to the host.

4. Treatment of hamsters infected with Leishmania donovani with combinations of sinefungin and any one of several selected purine analogs did not result in antileishmanial efficacy greater than that attributable to sinefungin alone.

5. The quaternary alkaloid, berberine, and three derivatives (8-cyanodihydroberberine, tetrahydroberberine, and n-methyltetrahydroberberinium iodide) had activity against L. donovani and berberine and one derivative (8-cyanodihydroberberine) had activity against L. braziliensis panamensis. Both antileishmanial activity and toxicity to the host appear to be associated with the presence of a quaternary nitrogen.

6. Liposome encapsulated amphotericin B was efficacious against L. donovani in both hamsters and squirrel monkeys at a therapeutic dosage found by others not to be toxic in human beings.

7. Of several hundred compounds studied sinefungin and WR06026 were the most active of the limited number of compounds noted to be suppressive against L. braziliensis panamensis. Most of the compounds found active against L. braziliensis panamensis were also toxic to the host.

LITERATURE CITED

1. Kinnamon, K. E., E. A. Steck, P. S. Loizeaux, L. D. Hendricks, V. B. Waits, W. L. Chapman, Jr., and W. L. Hanson. 1979. Leishmaniasis: Military significance and new hope for treatment. Mil. Med. 44(10): 660-664.

2. Tropical Disease Research, Seventh Programme Report, 1 January 1983 - 31 December 1984. UNDP/World Bank/WHO Imprimerie A. Barthelemy, Avignon, France 1985. Pages 7/3-7/18.

3. Biagi, F. 1976. Leishmaniasis. In Tropical Medicine, Hunter, G. H., J. C. Swartzwelder, and D. F. Clyde (Eds.) W. B. Saunders Co., Philadelphia. pp. 411-429.

4. Steck, E. A. 1972. The Chemotherapy of Protozoan Diseases. Walter Reed Army Institute of Research, Vol. II, Sect. 3, pp. 6.1-7.141, published by U. S. Govt. Printing Office.

5. Mahmoud, A. A. F., and K. S. Warren. 1977. Algorithms in the diagnosis and management of exotic diseases. XXIV. Leishmaniases. J. Infect. Dis. 136: 160-163.

6. Croft, S. L. 1988. Recent developments in the chemotherapy of leishmaniasis. Trends in Pharmacological Sciences. 9(10): 376-378.

7. Peters, W. 1981. The treatment of kala-azar - new approaches to an old problem. Indian J. Med. Res. 73(Suppl.): 1-18.

8. Perea, W. A. 1989. Epidemic visceral leishmaniasis in southern Sudan. The Lancet 2(8673): 1222.

9. Most, H. 1968. Leishmaniasis. In: Internal Medicine in World War II. Volume III. Infectious Diseases and General Medicine. Office of the Surgeon General, Department of the Army, Washington, D. C. pp. 1-48.

10. Naggan, L., A. E. Gunders, R. Dizian et al. 1970. Ecology and attempted control of cutaneous leishmaniasis around Jericho, in the Jordan Valley. J. Infect. Dis. 212: 427-432.

11. Walton, B. C., D. A. Person, and R. Bernstein. 1968. Leishmaniasis in the U. S. Military in the Canal Zone. Am. J. Trop. Med. Hyg. 17(1), 19-24.

12. Takafuji, E. T., L. D. Hendricks, J. L. Daubek, K. M. McNeil, H. W. Scagliola, and C. L. Diggs. 1980. Cutaneous leishmaniasis associated with jungle training. Am. J. Trop. Med. Hyg. 29(4): 516-520.

13. Neal, R. A. 1987. Experimental Chemotherapy. In: The Leishmaniases in Biology and Medicine. Vol. II. Clinical Aspects and Control. Peters, W. and Killick-Kendrick, R. (Eds.). Academic Press, London. pp. 793-845.

14. Bryceson, A. 1987. Therapy in Man. In: The Leishmaniases in Biology and Medicine. Vol. II. Clinical Aspects and Control. Peters, W. and Killick-Kendrick, R. (Eds.). Academic Press, London. pp. 847-907.

15. Hanson, W. L., V. B. Waits, L. D. Hendricks, W. T. Hockmeyer, D. E. Davidson, Jr., and W. L. Chapman, Jr. 1983. Relative insensitivity of a Kenyan strain of Leishmania donovani to pentavalent antimony therapy in hamsters. J. Parasitol. 69: 446.

16. Mebrahtu, Y., P. Lawyer, J. Githure, J. B. Were, R. Muigai, L. Hendricks, J. Leeuswenburg, D. Koech, and C. Roberts. 1989. Visceral leishmaniasis unresponsive to pentostam caused by Leishmania tropica in Kenya. Am. J. Trop. Med. Hyg. 41(3): 289-294.

17. Jackson, J. E., J. D. Tally, and D. B. Tang. 1989. An in vitro micromethod for drug sensitivity testing of Leishmania. Am. J. Trop. Med. Hyg. 41(3): 318-330.

18. WHO Publication TDR/CHEM LEISH/VL. 82.3. 1982. Report of the informal meeting on the chemotherapy of visceral leishmaniasis. p 4.

19. Stauber, L. A., E. M. Franchino, and J. Grun. 1958. An eight-day method for screening compounds against Leishmania donovani in the golden hamster. J. Protozool. 5: 269-273.

20. Stauber, L. A. 1958. Host resistance to the Khartoum strain of Leishmania donovani. The Rice Institute Pamphlet Vol. XLV(1): 80-96.

21. Stauber, L. A. 1958. Chemotherapy of experimental leishmaniasis. Proc. 6th International Congr. on Trop. Med. & Mal. III: 797-805.

22. Hanson, W. L., W. L. Chapman, Jr., and K. E. Kinnamon. 1977. Testing of drugs for antileishmanial activity in golden hamsters infected with Leishmania donovani. Internat'l. J. Parasitol. 7: 443-447.

23. Neal, R. A. and S. L. Croft. 1984. An in vitro system for determining the activity of compounds against the intracellular amastigote form of Leishmania donovani. J. Antimicro. Chem. 14: 463-475.

24. Hanson, W. L. and E. L. Roberson. 1974. Density of parasites in various organs and the relation to number of trypomastigotes in the blood during acute infections of Trypanosoma cruzi in mice. J. Protozool. 21: 512-517.

25. Hendricks, L. D., D. Wood, and M. Hajduk. 1978. Hemoflagellates: Commercially available liquid media for rapid cultivation. Parasitol. 76: 309-316.

26. Wilson, H. R., B. S. Dieckmann, and G. E. Childs. 1979. Leishmania braziliensis and Leishmania mexicana: Experimental cutaneous infections in golden hamsters. Exptl. Parasitol. 47: 270-283.

27. Berman, J. D., W. L. Hanson, W. L. Chapman, Jr., C. R. Alving, and G. Lopez-Berestein. 1986. Antileishmanial activity of liposome-encapsulated amphotericin B in the hamster and monkey. Antimicrobial Agents and Chemother. 30: 847-851.

28. Vennerstrom, J. L., J. K. Lovelace, V. B. Waits, W. L. Hanson, and D. L. Klayman. 1990. Berberine Derivatives as Antileishmanial Drugs. Antimicrobial Agents and Chemother. 34: 918-921.

29. Devi, A. C. 1929. Berberine sulfate in oriental sore. Indian Me Gazette 64: 139-140.

30. Berman, J. D., W. L. Hanson, J. K. Lovelace, V. B. Waits, J. E. Jackson, W. L. Chapman, Jr., and R. S. Klein. 1987. Activity of purine analogs against Leishmania donovani in vivo. Antimicrobial Agents and Chemother. 31(1): 111-113.

31. Chance, M. L. 1981. Leishmaniasis. Brit. Med. Bull. 283(7): 1245-1252.

32. Kinnamon, K. E., E. A. Steck, P. S. Loizeaux, W. L. Hanson, W. L. Chapman, Jr., and V. B. Waits. 1978. The antileishmanial activity of Lepidines. Am. J. Trop. Med. Hyg. 27(4): 751-757.

33. Hanson, W. L., V. B. Waits, and W. L. Chapman, Jr. Annual Report. February 28, 1989. Contract No. DAMD17-85-C-5012.

34. Nolan, L. Final Report. January 30, 1987. Contract No. DAMD17-81-1198.

35. Alving, C. R., E. A. Steck, W. L. Chapman, Jr., V. B. Waits, L. D. Hendricks, G. M. Swartz, Jr., and W. L. Hanson. 1980. Liposomes in leishmaniasis: Therapeutic effects of antimonial drugs, 8-aminoquinolines, and tetracycline. Life Sciences 26: 2231-2238.

36. DasGupta, B. M. and B. B. Dikshit. 1929. Berberine in treatment of oriental sore. Indian Med. Gazette 64: 67-70.

37. Ghosh, A. K., F. K. Bhattacharyya, and D. K. Ghosh. 1985. Leishmania donovani: Amastigote inhibition and mode of action of berberine. Exp. Parasitol. 60: 404-413.

38. Ghosh, A. K., M. M. Rakshit, and D. K. Ghosh. 1983. Effect of berberine chloride on Leishmania donovani. Indian J. Med. Res. 78: 407-416.

39. Karamchandani, P. V. 1927. An analysis of 337 cases of oriental sore treated by various methods. Indian Med. Gazette 62: 558.

40. Varma, R. L. 1927. Berberine sulfate in oriental sore. Indian Med. Gazette 62: 84-85.

41. Putzer, B. 1934. Berberine and its derivatives in the treatment of oriental sore. Med. Chem. Apsects. 2: 274-280.

42. El-on, J., G. P. Jacobs, E. Witztum, and C. L. Greenblatt. 1984. Development of topical treatment for cutaneous leishmaniasis caused by Leishmania major in experimental animals. Antimicrobial Agents and Chemother. 26: 745-751.

43. El-on, J., L. Weinrauch, R. Livshin, Z. Even-Paz, and G. P. Jacobs. 1985. Topical treatment of recurrent cutaneous leishmaniasis with ointment containing paromomycin and methylbenzethonium chloride. Br. Med. J. 291: 704-705.

44. Hanson, W. L. 1981. Chemotherapy and the immune response in protozoal infections. J. Protozool. 28(1): 27-30.

45. Adinolfi, L. E., P. F. Bonventre, M. V. Pas, and D. A. Eppstein. 1985. Synergistic effect of Glucantime and a liposome-encapsulated muramyl dipeptide analog in therapy of experimental visceral leishmaniasis. Infect. and Immun. 48(2): 409-416.

Appendix 1

TABLE I. Summary of compounds found to be active in the primary visceral test system.

BN	DOSE1	SUPPRES1	DOSE2	SUPPRES2	DOSE3	SUPPRES3	SD50	SD50GLU	GI
BK01845	.4	93	6.4	100	NDNDN	NDN	.273	212	773.
BK99014	.4	70	6.4	100	NDNDN	NDN	.354	212	597.
BK99014	.4	20	6.4	100	NDNDN	NDN	1.39	212	151.
BK01845	0.2	50	0.8	95	3.2	100	40.4	40	.999
BK01845	0.2	56	0.8	92	3.2	99	.192	40	209.
BK99014	0.2	- 13	0.8	72	3.2	99	.699	40	57.7
BK99014	0.8	19	3.2	95	13	100	.993	40	40.6
BK73823	52	34	208	52	832	53	190.	45	.234
BK73832	52	16	208	15	832	54	767.	45	.058
BK73841	52	34	208	69	832	68	123.	45	.362
BK84237	52	- 9	208	22	832	50	NDND	NDN	NDND
BK84246	52	46	208	52	832	63	155.	45	.286
BK85510	52	86	208	99	832	NDN	29.9	45	1.48
BK86106	52	27	208	31	832	57	663.	45	.067
BL05848	52	100	208	100	832	NDN	23.7	45	1.87
BK01845	.2	38	1.62	98	13	100	.215	28	131.
BK01845	.2	59	1.62	100	13	100	.190	28	148.
BK70411	52	32	208	49	832	67	242.	16	.065
BK84200	52	100	208	99	832	NDN	22.0	16	.722
BK95132	52	35	208	50	832	77	330.	16	.048
BK95150	52	38	208	43	832	62	437.	16	.036
BK95221	52	9	208	37	832	64	508.	16	.031
BK57301	52	50	208	69	832	79	51.7	16	.308
BK95230	52	42	208	60	832	58	121.	16	.131
BK95258	52	28	208	55	832	68	178.	16	.089
BL03808	52	100	208	100	832	NDN	23.1	16	.689
BL07682	52	100	208	100	832	NDN	23.0	16	.693
BL05848	13	99	52	99	208	NDN	4.92	41	8.26
ZP23714	3.25	- 47	13	69	52	99	9.93	41	4.09
ZP43261	3.25	3	13	97	52	100	6.61	41	6.15
ZP46833	3.25	13	13	48	52	100	12.7	41	3.18
BL07931	52	20	208	72	832	95	140.	51	.36
BL10956	6.5	60	52	85	104	94	4.36	18	4.04
BL12521	26	56	104	78	208	83	22.5	18	.784
BK46362	26	27	52	53	208	75	51.0	18	.345
BH32724	1.6	21	3.2	15	13	85	6.27	18	2.82
BK01845	.102	20	.203	51	.812	99	.201	18	87.8
AV95898	52	59	416	62	NDNDN	NDN	43.8	29	.659
AV96091	52	39	416	68	NDNDN	NDN	189.	29	.152
AV98031	52	46	416	65	NDNDN	NDN	128.	29	.225
AV98111	52	24	416	56	NDNDN	NDN	347.	29	.083
AV99930	52	47	416	55	NDNDN	NDN	188.	29	.153
AW04007	52	42	416	70	NDNDN	NDN	155.	19	.119
AW03902	52	41	416	57	NDNDN	NDN	256.	19	.072
AW03984	52	32	416	63	NDNDN	NDN	263.	19	.07
AW03797	52	37	416	66	NDNDN	NDN	214.	19	.086
BL20345	52	10	208	36	832	72	450.	40	.089

TABLE I. (Continued)

BK99121	52	99	416	NDN	NDNDN	NDN	25.4	35	1.38
BL07502	52	22	208	85	NDNDN	NDN	120.	39	.32
BL11864	52	100	208	NDN	832	NDN	25.1	205	8.13
BL09533	52	12	208	72	NDNDN	NDN	148.	205	1.37
BL12503	3.25	42	13	43	52	50	NDND	205	NDND
BL20649	52	93	416	100	NDNDN	NDN	27.2	32	1.17
BL20603	52	20	416	57	NDNDN	NDN	346.	32	.092
BL20587	52	26	416	51	NDNDN	NDN	405.	32	.078
BL20596	52	41	416	71	NDNDN	NDN	160.	32	.198
BL19324	52	31	416	59	NDNDN	NDN	298.	32	.106
BL19315	52	38	416	67	NDNDN	NDN	202.	32	.157
BL22590	52	13	208	62	NDNDN	NDN	169.	102	.601
BL22741	52	13	208	59	NDNDN	NDN	81.8	82	.999
BL22876	52	46	208	52	NDNDN	NDN	155.	54	.348
BL22910	52	30	208	73	NDNDN	NDN	122.	111	.906
BL31839	.203	51	.812	62	3.25	72	.201	0	.748
BL34296	.203	8	.812	63	3.25	97	.751	0	.201
BL25144	52	1	208	54	NDNDN	NDN	196.	48	.244
BL11104	52	24	104	21	208	91	145.	60	.409
BL11113	52	64	104	68	208	92	39.5	60	1.50
BL27666	52	18	208	58	NDNDN	NDN	176.	44	.247
BL28378	52	18	208	58	NDNDN	NDN	176.	30	.171
BL32292	52	21	208	52	NDNDN	NDN	197.	33	.165
BL32309	52	14	208	52	NDNDN	NDN	199.	33	.164
BL32550	52	17	208	56	NDNDN	NDN	183.	33	.178
BL33735	52	14	208	58	NDNDN	NDN	179.	26	.144
BL34938	52	7	208	50	NDNDN	NDN	NDND	80	NDND
BL34929	52	41	208	50	NDNDN	NDN	NDND	36	NDND
BL10885	52	83	104	87	NDNDN	NDN	25.2	126	4.98
ZP33121	52	61	208	83	NDNDN	NDN	41.9	126	2.99
BL51297	52	100	208	NDN	832	NDN	25.0	26	1.03
BL50021	52	100	208	100	416	NDN	25.0	26	1.03
BL51304	52	86	208	NDN	832	NDN	29.9	26	.865
BL49993	52	100	208	100	416	100	25.1	26	1.02
BL37135	52	30	208	61	NDNDN	NDN	152.	60	.396
BL38589	52	19	208	50	NDNDN	NDN	NDND	31	NDND
BL52749	52	100	208	100	NDNDN	NDN	25.1	24	.952
AJ07615	52	27	208	55	NDNDN	NDN	179.	24	.133
BG56265	52	100	208	100	NDNDN	NDN	25.1	24	.952
BL53308	52	100	208	99	NDNDN	NDN	25.1	26	1.03
BL55928	52	67	208	NDN	NDNDN	NDN	38.4	79	2.06
ZP30451	52	100	208	NDN	NDNDN	NDN	25.0	79	3.17
BL05848	0.20	4	0.81	20	3.25	64	39.6	40	1
BL07682	0.20	4	0.81	18	3.25	90	39.6	40	1
BL07682	0.20	13	0.81	12	3.25	85	39.6	40	1
BL49993	0.20	9	0.81	34	3.25	68	39.6	40	1

TABLE II. Summary of compounds found to be inactive in the primary visceral test system.

BN	DOSE1	SUPPRES1	DOSE2	SUPPRES2	DOSE3	SUPPRES3
BK84237	52	-9	208	22	832	50
BK84255	52	16	208	36	832	31
BK84264	52	13	208	25	832	32
BK86115	52	25	208	30	832	32
BL05884	.2	7	1.62	18	13	33
BL05884	.2	-1	1.62	8	13	0
BK95249	52	38	208	36	832	47
BK95212	52	43	208	43	832	46
AW04794	52	-15	416	6	NDNDN	NDN
AW04801	52	-16	416	-47	NDNDN	NDN
AW05166	52	-2	416	5	NDNDN	NDN
AW05175	52	-8	416	-23	NDNDN	NDN
AW05193	52	-8	416	35	NDNDN	NDN
AW05200	52	-20	416	-8	NDNDN	NDN
AW05255	52	-29	416	10	NDNDN	NDN
AW05273	52	-9	416	20	NDNDN	NDN
AW05282	52	5	416	20	NDNDN	NDN
AW05291	52	14	416	NDN	NDNDN	NDN
BK95178	52	-46	208	-1	832	-19
BK95196	52	-17	208	-24	832	35
BK96139	52	-20	208	-27	832	-8
BK96148	52	-21	208	-1	832	27
AW05308	52	4	416	-33	NDNDN	NDN
AW05326	52	-12	416	7	NDNDN	NDN
AW05371	52	-15	416	-5	NDNDN	NDN
AW05380	52	20	416	-28	NDNDN	NDN
AW05399	52	-14	416	-7	NDNDN	NDN
AW05451	52	-10	416	3	NDNDN	NDN
AW05488	52	-14	416	-3	NDNDN	NDN
AW05504	52	1	416	-9	NDNDN	NDN
AW05513	52	-11	416	2	NDNDN	NDN
AW05522	52	3	416	0	NDNDN	NDN
AW05531	52	-4	416	-9	NDNDN	NDN
BL07888	52	-6	208	7	832	39
BL07904	52	-7	208	12	832	14
BL07913	52	-21	208	2	832	-1
BL07922	52	-34	208	-3	832	-5
BL07940	52	-6	208	5	832	-2
BL07959	52	-18	208	-11	832	-15
BL07968	52	-16	208	-37	832	10
BL07977	52	-35	208	-13	832	-13
BL07986	52	-20	208	-14	832	16
BL09686	52	-7	208	35	832	NDN
AJ28445	52	24	416	37	NDNDN	NDN
AL69419	52	12	416	-6	NDNDN	NDN
AR98988	52	29	416	-6	NDNDN	NDN
AS38423	52	21	416	28	NDNDN	NDN
AS87613	52	0	416	29	NDNDN	NDN

TABLE II. (Continued)

AW05568	52	5	416	- 13	NDNDN	NDN
BK22175	52	13	208	23	832	39
BK75050	52	16	416	NDN	NDNDN	NDN
BK75069	52	7	416	NDN	NDNDN	NDN
BK75103	52	13	416	NDN	NDNDN	NDN
BK75121	52	- 3	416	30	NDNDN	NDN
BL09337	416	NDN	NDNDN	NDN	NDNDN	NDN
BL09828	52	- 3	208	7	416	- 9
BL11364	52	- 14	416	21	NDNDN	NDN
AU91073	52	- 4	416	- 13	NDNDN	NDN
AV78324	52	- 21	416	13	NDNDN	NDN
AV79170	52	- 28	416	- 9	NDNDN	NDN
AV79456	52	- 29	416	- 35	NDNDN	NDN
AV79518	52	1	416	1	NDNDN	NDN
AV79563	52	- 18	416	2	NDNDN	NDN
AV88571	52	- 16	416	18	NDNDN	NDN
AW05577	52	- 8	416	14	NDNDN	NDN
BK96157	52	- 32	208	- 13	832	- 20
BL09837	52	- 23	208	- 19	832	10
BL09846	52	- 6	208	- 11	832	NDN
BL10590	52	- 49	208	- 9	832	- 23
BL10607	52	- 6	208	9	832	- 1
BL10714	52	- 32	208	- 20	832	- 51
AV93876	52	8	416	13	NDNDN	NDN
AV93929	52	0	416	8	NDNDN	NDN
AV93938	52	3	416	- 16	NDNDN	NDN
AV93956	52	- 5	416	- 2	NDNDN	NDN
AV95503	52	- 2	416	- 11	NDNDN	NDN
AV95656	52	- 7	416	- 5	NDNDN	NDN
AV95665	52	- 1	416	NDN	NDNDN	NDN
AV95683	52	- 7	416	- 3	NDNDN	NDN
AV95736	52	16	416	NDN	NDNDN	NDN
BK98768	52	- 11	416	39	NDNDN	NDN
BK40431	52	- 22	208	- 15	832	8
BK40422	52	32	208	29	832	17
AV97543	52	18	416	25	NDNDN	NDN
AW03019	52	8	416	13	NDNDN	NDN
AW03028	52	4	416	0	NDNDN	NDN
AW03402	52	16	416	39	NDNDN	NDN
AW03493	52	4	416	42	NDNDN	NDN
AW03877	52	4	416	19	NDNDN	NDN
AW03635	52	36	416	24	NDNDN	NDN
AW03886	52	15	416	42	NDNDN	NDN
AW03733	52	42	416	43	NDNDN	NDN
AW03206	52	6	416	17	NDNDN	NDN
AW03466	52	27	416	33	NDNDN	NDN
AW03617	52	14	416	- 9	NDNDN	NDN
AW03911	52	37	416	40	NDNDN	NDN
AW03939	52	15	416	33	NDNDN	NDN
AW03975	52	39	416	NDN	NDNDN	NDN

TABLE II. (Continued)

AW04025	52	31	416	38	NDNDN	NDN
AW04034	104	- 7	832	- 1	NDNDN	NDN
AW04070	52	9	416	0	NDNDN	NDN
AW07204	52	2	416	0	NDNDN	NDN
AW07213	52	5	416	6	NDNDN	NDN
AW07222	52	4	416	13	NDNDN	NDN
AW07231	52	- 1	416	6	NDNDN	NDN
AW07240	52	8	416	- 1	NDNDN	NDN
AW07259	52	8	416	1	NDNDN	NDN
BK40413	52	- 1	208	14	832	4
BK40440	52	1	208	7	584	2
BK40459	52	5	208	5	832	- 3
BK40799	52	1	208	9	832	9
AW07268	52	- 5	416	7	NDNDN	NDN
AW07277	52	1	416	15	NDNDN	NDN
AW07295	52	4	416	2	NDNDN	NDN
BL20336	52	11	208	0	832	36
BL20354	52	2	208	- 4	832	35
AW07302	52	19	416	29	NDNDN	NDN
AW07311	52	- 10	416	11	NDNDN	NDN
AW07320	52	13	416	25	NDNDN	NDN
AW07339	52	- 22	416	- 8	NDNDN	NDN
AW07348	52	- 2	416	25	NDNDN	NDN
AW07366	52	- 17	416	43	NDNDN	NDN
AW07375	52	38	416	7	NDNDN	NDN
AW07384	52	- 12	416	13	NDNDN	NDN
AW07393	52	36	416	21	NDNDN	NDN
AW07400	52	- 22	416	30	NDNDN	NDN
AW07419	52	- 5	416	19	NDNDN	NDN
AW07428	52	18	416	31	NDNDN	NDN
AW10096	52	26	416	NDN	NDNDN	NDN
AW07437	52	- 4	416	- 4	NDNDN	NDN
AW07455	52	- 22	416	10	NDNDN	NDN
AW07517	52	9	416	4	NDNDN	NDN
AW07473	52	17	416	24	NDNDN	NDN
AW07526	52	18	416	14	NDNDN	NDN
AW07491	52	7	416	14	NDNDN	NDN
AW07508	52	1	416	17	NDNDN	NDN
AW07446	52	- 1	416	25	NDNDN	NDN
AW07464	52	- 13	416	15	NDNDN	NDN
AW07535	52	- 7	416	25	NDNDN	NDN
AW07544	52	6	416	- 16	NDNDN	NDN
AW07553	52	- 4	416	5	NDNDN	NDN
AW07562	52	5	416	- 11	NDNDN	NDN
AW10103	52	- 29	416	9	NDNDN	NDN
AW10130	52	- 28	416	- 26	NDNDN	NDN
AW10185	52	- 46	416	- 25	NDNDN	NDN
AW10158	52	- 13	416	- 17	NDNDN	NDN
AW10201	52	- 32	416	- 21	NDNDN	NDN
AW10167	52	- 17	416	- 2	NDNDN	NDN

TABLE II. (Continued)

AW10176	52	- 56	416	- 24	NDNDN	NDN
AW10121	52	- 37	416	10	NDNDN	NDN
AW10149	52	- 35	416	1	NDNDN	NDN
AW10238	52	- 36	416	- 30	NDNDN	NDN
AW10247	52	- 26	416	- 6	NDNDN	NDN
AW10256	52	- 34	416	- 33	NDNDN	NDN
AW10265	52	- 23	416	- 44	NDNDN	NDN
AW05595	52	- 9	416	0	NDNDN	NDN
AW06663	52	8	416	4	NDNDN	NDN
AW06725	52	4	416	3	NDNDN	NDN
AW06681	52	3	416	- 5	NDNDN	NDN
AW06734	52	4	416	8	NDNDN	NDN
AW06707	52	1	416	3	NDNDN	NDN
AW06743	52	- 2	416	6	NDNDN	NDN
AW06716	52	- 1	416	7	NDNDN	NDN
AW06654	52	- 2	416	13	NDNDN	NDN
AW06672	52	- 9	416	- 1	NDNDN	NDN
AW06690	52	9	416	2	NDNDN	NDN
AW06752	52	1	416	5	NDNDN	NDN
AW06761	52	8	416	- 2	NDNDN	NDN
AW06770	52	- 1	416	5	NDNDN	NDN
AW06789	52	8	416	6	NDNDN	NDN
AW06805	52	9	416	3	NDNDN	NDN
AW06823	52	24	416	31	NDNDN	NDN
AW06903	52	11	416	15	NDNDN	NDN
AW06850	52	- 5	416	21	NDNDN	NDN
AW06912	52	- 13	416	28	NDNDN	NDN
AW06878	52	14	416	43	NDNDN	NDN
AW06921	52	- 11	416	21	NDNDN	NDN
AW06887	52	11	416	5	NDNDN	NDN
AW06814	52	- 15	416	21	NDNDN	NDN
AW06832	52	- 31	416	- 8	NDNDN	NDN
AW06869	52	28	416	17	NDNDN	NDN
AW06930	52	32	416	24	NDNDN	NDN
AW06949	52	24	416	9	NDNDN	NDN
AW06967	52	15	416	- 14	NDNDN	NDN
AW06976	52	9	416	20	NDNDN	NDN
AW06985	52	- 28	416	7	NDNDN	NDN
AW07008	52	- 10	416	- 16	NDNDN	NDN
AW07017	52	- 2	416	- 7	NDNDN	NDN
AW07026	52	- 18	416	3	NDNDN	NDN
AW07035	52	- 7	416	6	NDNDN	NDN
AW07044	52	- 5	416	10	NDNDN	NDN
AW07071	52	0	416	27	NDNDN	NDN
AW07080	52	5	416	20	NDNDN	NDN
AW07099	52	- 2	416	4	NDNDN	NDN
AW07106	52	16	416	38	NDNDN	NDN
AW07115	52	15	416	18	NDNDN	NDN
AW07124	52	7	416	16	NDNDN	NDN
AW07133	52	8	416	28	NDNDN	NDN

TABLE II. (Continued)

AW07151	52 6	416 19	NDNDN	NDN
AW07160	52 7	416 14	NDNDN	NDN
AW07179	52 1	416 - 7	NDNDN	NDN
AW07188	52 39	416 28	NDNDN	NDN
AW07197	52 36	416 42	NDNDN	NDN
BK98777	52 22	416 NDN	NDNDN	NDN
BK98786	52 18	416 24	NDNDN	NDN
BK98795	52 - 3	416 40	NDNDN	NDN
BK98802	52 - 13	416 42	NDNDN	NDN
BL00432	52 21	416 32	NDNDN	NDN
BL01500	52 7	416 11	NDNDN	NDN
BL01519	52 49	416 46	NDNDN	NDN
BL07440	52 31	208 49	NDNDN	NDN
BL08401	52 11	416 18	NDNDN	NDN
BL07468	52 26	208 39	NDNDN	NDN
BL07600	52 - 2	208 10	NDNDN	NDN
BL07486	52 21	208 46	NDNDN	NDN
BL07619	52 - 9	208 3	NDNDN	NDN
BL07557	52 - 6	208 18	NDNDN	NDN
BL07520	52 9	208 19	NDNDN	NDN
BL07566	52 28	208 34	NDNDN	NDN
BL07539	52 18	208 18	NDNDN	NDN
BL07548	52 9	208 11	NDNDN	NDN
BL07495	52 17	208 44	NDNDN	NDN
BL07511	52 22	208 - 15	NDNDN	NDN
BL07575	52 - 1	208 42	NDNDN	NDN
BL07584	52 13	208 12	NDNDN	NDN
BL07593	52 - 23	208 20	NDNDN	NDN
BL07459	52 31	208 40	NDNDN	NDN
BL07477	52 35	208 32	NDNDN	NDN
BL09524	52 - 19	208 - 21	NDNDN	NDN
AC43817	52 - 12	416 - 9	NDNDN	NDN
BL11846	52 - 54	208 22	832	NDN
BL09373	13 - 69	52 - 34	NDNDN	NDN
BL10796	52 - 46	208 - 41	416	- 1
BL12503	3.25 - 42	13 - 43	52	50
AX27014	52 0	416 19	NDNDN	NDN
BL09597	52 NDN	416 NDN	NDNDN	NDN
BL11373	52 25	416 25	NDNDN	NDN
BL11382	52 4	416 0	NDNDN	NDN
BL11391	52 19	416 30	NDNDN	NDN
BL22072	52 23	416 34	NDNDN	NDN
BL21155	52 27	416 34	NDNDN	NDN
BL22143	52 15	416 10	NDNDN	NDN
BL19333	52 15	416 41	NDNDN	NDN
BL12790	52 NDN	416 NDN	NDNDN	NDN
AG72747	104 - 24	208 - 77	416	- 61
BL26847	104 9	208 11	416	11
BL26865	104 - 19	208 - 19	416	6
BL24174	52 - 26	416 NDN	NDNDN	NDN

TABLE II. (Continued)

BL22081	52	15	416	22	NDNDN	NDN
BL24209	52	- 9	416	5	NDNDN	NDN
BL24227	52	14	416	22	NDNDN	NDN
BL22107	52	1	416	12	NDNDN	NDN
BL24236	52	- 32	416	- 29	NDNDN	NDN
BL23864	52	- 3	416	16	NDNDN	NDN
BL24245	52	28	416	37	NDNDN	NDN
BL22090	52	- 2	416	26	NDNDN	NDN
BL23873	52	- 3	416	2	NDNDN	NDN
BL24218	52	24	416	43	NDNDN	NDN
BL23882	52	- 13	416	6	NDNDN	NDN
BL22116	52	9	416	45	NDNDN	NDN
BL24254	52	- 1	416	- 14	NDNDN	NDN
BL22518	52	- 5	208	5	NDNDN	NDN
BL22527	52	- 12	208	- 21	NDNDN	NDN
BL22607	52	21	208	23	NDNDN	NDN
BL22545	52	- 7	208	21	NDNDN	NDN
BL22616	52	- 8	208	13	NDNDN	NDN
BL22563	52	- 10	208	2	NDNDN	NDN
BL22581	52	- 6	208	13	NDNDN	NDN
BL22536	52	12	208	26	NDNDN	NDN
BL22554	52	10	208	- 7	NDNDN	NDN
BL22572	52	0	208	48	NDNDN	NDN
BK57276	52	- 27	208	33	832	15
BL22625	52	- 23	208	2	NDNDN	NDN
BL22634	52	0	208	- 1	NDNDN	NDN
BL22643	52	- 8	208	- 48	NDNDN	NDN
BL22652	52	- 23	208	32	NDNDN	NDN
BL22732	52	6	208	24	NDNDN	NDN
BL22661	52	- 5	208	16	NDNDN	NDN
BL22689	52	- 18	208	NDN	NDNDN	NDN
BL22750	52	18	208	- 38	NDNDN	NDN
BL22705	52	- 10	208	- 36	NDNDN	NDN
BL22723	52	0	208	- 28	NDNDN	NDN
BL22670	52	- 11	208	6	NDNDN	NDN
BL22698	52	- 32	208	- 25	NDNDN	NDN
BL22714	52	9	208	- 30	NDNDN	NDN
BL22769	52	23	208	48	NDNDN	NDN
BL22778	52	18	208	41	NDNDN	NDN
BL22787	52	29	208	43	NDNDN	NDN
BL22796	52	20	208	35	NDNDN	NDN
BL22803	52	27	208	43	NDNDN	NDN
BL22885	52	26	208	39	NDNDN	NDN
BL22812	52	15	208	42	NDNDN	NDN
BL22894	52	31	208	46	NDNDN	NDN
BL22830	52	20	208	35	NDNDN	NDN
BL22901	52	26	208	39	NDNDN	NDN
BL22858	52	28	208	41	NDNDN	NDN
BL22821	52	26	208	42	NDNDN	NDN
BL22849	52	22	208	49	NDNDN	NDN

TABLE II. (Continued)

BL22867	52	28	208	40	NDNDN	NDN
BL22929	52	20	208	15	NDNDN	NDN
BL22938	52	14	208	2	NDNDN	NDN
BL22947	52	31	208	22	NDNDN	NDN
BL22956	52	32	208	30	NDNDN	NDN
BL23033	52	20	208	-7	NDNDN	NDN
BL22965	52	0	208	-4	NDNDN	NDN
BL23042	52	23	208	21	NDNDN	NDN
BL22983	52	-4	208	38	NDNDN	NDN
BL23051	52	7	208	31	NDNDN	NDN
BL23006	52	11	208	21	NDNDN	NDN
BL23024	52	17	208	25	NDNDN	NDN
BL22974	52	1	208	29	NDNDN	NDN
BL22992	52	10	208	22	NDNDN	NDN
BL23015	52	13	208	22	NDNDN	NDN
BL23060	52	5	208	19	NDNDN	NDN
BL23088	52	-11	208	10	NDNDN	NDN
BL23097	52	16	208	25	NDNDN	NDN
BL23104	52	-21	208	26	NDNDN	NDN
BL23113	52	-28	208	-23	NDNDN	NDN
BL23195	52	-10	208	32	NDNDN	NDN
BL23122	52	7	208	21	NDNDN	NDN
BL23202	52	11	208	32	NDNDN	NDN
BL23140	52	-33	208	-14	NDNDN	NDN
BL23211	52	42	208	NDN	NDNDN	NDN
BL23168	52	5	208	28	NDNDN	NDN
BL23186	52	-26	208	36	NDNDN	NDN
BL23131	52	-22	208	-8	NDNDN	NDN
BL23159	52	21	208	NDN	NDNDN	NDN
BL23177	52	-20	208	-11	NDNDN	NDN
BL23220	52	-31	208	23	NDNDN	NDN
BL23239	52	-43	208	-29	NDNDN	NDN
BL23248	52	-2	208	13	NDNDN	NDN
BL23257	52	27	208	22	NDNDN	NDN
BL23266	52	5	208	-4	NDNDN	NDN
BL23355	52	8	208	6	NDNDN	NDN
BL23275	52	13	208	27	NDNDN	NDN
BL23364	52	-5	208	21	NDNDN	NDN
BL23293	52	0	208	4	NDNDN	NDN
BL23373	52	-13	208	-2	NDNDN	NDN

TABLE II. (Continued)

BL23319	52	6	208	14	NDNDN	NDN
BL23346	52	8	208	-17	NDNDN	NDN
BL23284	52	-1	208	18	NDNDN	NDN
BL23300	52	-5	208	-9	NDNDN	NDN
BL23328	52	4	208	15	NDNDN	NDN
BL23382	52	-3	208	9	NDNDN	NDN
BL23391	52	4	208	17	NDNDN	NDN
BL23408	52	-9	208	4	NDNDN	NDN
BL23417	52	-40	208	-10	NDNDN	NDN
BL23426	52	-37	208	3	NDNDN	NDN
BL23506	52	9	208	17	NDNDN	NDN
BL23435	52	-12	208	-8	NDNDN	NDN
BL23524	52	6	208	33	NDNDN	NDN
BL23453	52	-2	208	25	NDNDN	NDN
BL24530	52	-67	208	-9	NDNDN	NDN
BL23471	52	-8	208	24	NDNDN	NDN
BL23499	52	-3	208	7	NDNDN	NDN
BL23444	52	-24	208	-21	NDNDN	NDN
BL23462	52	-25	208	5	NDNDN	NDN
BL23480	52	-4	208	21	NDNDN	NDN
BL24549	52	11	208	21	NDNDN	NDN
BL24558	52	-30	208	-10	NDNDN	NDN
BL24567	52	-41	208	-23	NDNDN	NDN
BL24576	208	33	523	7	NDNDN	NDN
BL24585	52	-19	208	17	NDNDN	NDN
BL24665	52	8	208	16	NDNDN	NDN
BL24594	52	5	208	19	NDNDN	NDN
BL24674	52	14	208	20	NDNDN	NDN
BL24610	52	0	208	3	NDNDN	NDN
BL24683	52	2	208	5	NDNDN	NDN
BL24638	52	-12	208	24	NDNDN	NDN
BL24656	52	20	208	NDN	NDNDN	NDN
BL24601	52	8	208	26	NDNDN	NDN
BL24629	52	-1	208	14	NDNDN	NDN
BL24647	52	4	208	17	NDNDN	NDN
BL24692	52	-5	208	14	NDNDN	NDN
BL24709	52	-3	208	10	NDNDN	NDN
BL24718	52	21	208	NDN	NDNDN	NDN
BL24727	52	-4	208	18	NDNDN	NDN
BL24736	52	-2	208	4	NDNDN	NDN
BL24816	52	7	208	23	NDNDN	NDN
BL24745	52	6	208	25	NDNDN	NDN
BL24825	52	-17	208	6	NDNDN	NDN
BL24763	52	3	208	10	NDNDN	NDN
BL24834	52	-37	208	15	NDNDN	NDN
BL24781	52	-12	208	5	NDNDN	NDN
BL24807	52	-5	208	15	NDNDN	NDN
BL24754	52	-5	208	15	NDNDN	NDN
BL24772	52	-14	208	-11	NDNDN	NDN
BL24790	52	16	208	21	NDNDN	NDN

TABLE II. (Continued)

BL24843	52 - 12	208 - 2	NDNDN	NDN
BL24852	52 - 11	208 - 7	NDNDN	NDN
BL24861	52 1	208 - 16	NDNDN	NDN
BL24870	52 - 35	208 15	NDNDN	NDN
BL24889	52 - 14	208 - 33	NDNDN	NDN
BL24898	52 9	208 2	NDNDN	NDN
BL24905	52 - 15	208 - 19	NDNDN	NDN
BL24914	52 - 5	208 11	NDNDN	NDN
BL24923	52 - 22	208 6	NDNDN	NDN
BL24932	52 - 17	208 - 9	NDNDN	NDN
BL24941	52 - 29	208 5	NDNDN	NDN
BL24950	52 2	208 34	NDNDN	NDN
BL24969	52 - 13	208 8	NDNDN	NDN
BL24978	52 - 5	208 22	NDNDN	NDN
BL24987	52 - 10	208 17	NDNDN	NDN
BL24996	52 13	208 26	NDNDN	NDN
BL25000	52 - 12	208 27	NDNDN	NDN
BL25019	52 17	208 20	NDNDN	NDN
BL25028	52 - 23	208 - 10	NDNDN	NDN
BL25037	52 - 15	208 19	NDNDN	NDN
BL25046	52 2	208 6	NDNDN	NDN
BL25055	52 8	208 17	NDNDN	NDN
BL25064	52 0	208 - 5	NDNDN	NDN
BL25073	52 - 9	208 - 5	NDNDN	NDN
BL25082	52 - 9	208 25	NDNDN	NDN
BL25091	52 8	208 36	NDNDN	NDN
BL25108	52 - 1	208 12	NDNDN	NDN
BL25117	52 - 14	208 11	NDNDN	NDN
BL25126	52 - 34	208 - 14	NDNDN	NDN
BL25135	52 - 27	208 0	NDNDN	NDN
BL25215	52 - 42	208 - 17	NDNDN	NDN
BL25153	52 - 37	208 - 24	NDNDN	NDN
BL25171	52 - 42	208 - 5	NDNDN	NDN
BL25224	52 - 27	208 - 8	NDNDN	NDN
BL25180	52 - 40	208 - 22	NDNDN	NDN
BL25199	52 5	208 22	NDNDN	NDN
BL25206	52 - 40	208 - 21	NDNDN	NDN
BL25162	52 - 36	208 - 1	NDNDN	NDN
BL25233	52 - 3	208 12	NDNDN	NDN
BL25242	52 - 22	208 10	NDNDN	NDN
BL25251	52 - 19	208 2	NDNDN	NDN
BL25260	52 - 33	208 - 3	NDNDN	NDN
BL25279	52 - 17	208 35	NDNDN	NDN
BL25288	52 - 27	208 - 8	NDNDN	NDN
BL25368	52 26	208 NDN	NDNDN	NDN
BL25297	52 - 16	208 23	NDNDN	NDN
BL25313	52 - 48	208 - 5	NDNDN	NDN
BL25322	52 - 16	208 0	NDNDN	NDN
BL25331	52 - 23	208 49	NDNDN	NDN
BL25340	52 - 45	208 - 14	NDNDN	NDN

TABLE II. (Continued)

BL25359	52	-26	208	-20	NDNDN	NDN
BL25304	52	-5	208	19	NDNDN	NDN
BL25377	52	45	208	NDN	NDNDN	NDN
BL25386	52	4	208	-9	NDNDN	NDN
BL25395	52	1	208	38	NDNDN	NDN
BL25402	52	-4	208	16	NDNDN	NDN
BL25411	52	0	208	21	NDNDN	NDN
BL25420	52	7	208	16	NDNDN	NDN
BL25439	52	-8	208	16	NDNDN	NDN
BL25519	52	-18	208	31	NDNDN	NDN
BL25448	52	8	208	37	NDNDN	NDN
BL25466	52	18	208	19	NDNDN	NDN
BL25475	52	-7	208	18	NDNDN	NDN
BL25484	52	-19	208	-8	NDNDN	NDN
BL25493	52	-17	208	-12	NDNDN	NDN
BL25500	52	9	208	13	NDNDN	NDN
BL25457	52	-5	208	14	NDNDN	NDN
BL25528	52	-5	208	25	NDNDN	NDN
BL25733	52	-1	208	37	NDNDN	NDN
BL25742	52	4	208	12	NDNDN	NDN
BL25751	52	5	208	-5	NDNDN	NDN
BL25760	52	-35	208	-4	NDNDN	NDN
BL25779	52	-26	208	-2	NDNDN	NDN
BL25788	52	-25	208	32	NDNDN	NDN
BL25868	52	3	208	32	NDNDN	NDN
BL25797	52	4	208	39	NDNDN	NDN
BL25813	52	-18	208	-25	NDNDN	NDN
BL25822	52	-18	208	45	NDNDN	NDN
BL25831	52	-11	208	8	NDNDN	NDN
BL25840	52	-16	208	15	NDNDN	NDN
BL25859	52	-2	208	-12	NDNDN	NDN
BL25804	52	-14	208	5	NDNDN	NDN
BL25877	52	-14	208	2	NDNDN	NDN
BL25886	52	2	208	14	NDNDN	NDN
BL25895	52	0	208	7	NDNDN	NDN
BL25902	52	5	208	1	NDNDN	NDN
BL25911	52	-11	208	5	NDNDN	NDN
BL25920	52	1	208	5	NDNDN	NDN
BL25939	52	6	208	-1	NDNDN	NDN
BL26016	52	8	208	-1	NDNDN	NDN
BL25948	52	8	208	-2	NDNDN	NDN
BL26025	52	-9	208	4	NDNDN	NDN
BL25966	52	8	208	16	NDNDN	NDN
BL25984	52	9	208	15	NDNDN	NDN
BL25993	52	12	208	3	NDNDN	NDN
BL26007	52	-1	208	-13	NDNDN	NDN
BL25957	52	9	208	-1	NDNDN	NDN
BL25975	52	6	208	-7	NDNDN	NDN
BL31099	52	4	208	4	416	34
BL31106	52	15	208	29	416	26

TABLE II. (Continued)

BL31115	52	-3	208	3	416	1
BL31124	52	-6	208	-12	416	0
BL31133	52	5	208	17	416	-1
BL31142	52	-10	208	-3	416	20
BL31151	52	-1	208	-25	416	3
BL31160	52	16	208	14	416	13
BL31179	52	23	208	21	416	19
BL31188	13	3	52	4	208	13
BL31197	52	14	208	23	416	48
BL31204	52	6	208	18	416	25
BL31213	52	6	208	3	416	12
BL31222	52	-17	208	10	416	10
BL31231	52	-1	208	-11	416	12
BL31240	52	-11	208	-9	416	3
BL31259	52	4	208	-4	416	-11
BL31268	52	-3	208	1	416	-8
BL31277	52	-7	208	-5	416	-10
BL31286	52	-11	208	2	416	-9
BL31295	52	-3	208	1	416	6
BL31302	52	-6	208	3	416	-8
BL31311	52	-3	208	-6	416	5
BL31320	52	-1	208	-15	416	28
BL31339	52	-4	208	2	416	4
BL31348	52	-5	208	2	416	-13
BL31357	52	-9	208	-2	416	12
BL31446	52	-8	208	-4	416	-20
BL31366	52	-7	208	-1	416	-10
BL31455	52	0	208	-9	416	-16
BL31384	52	-3	208	0	416	-11
BL31464	52	-4	208	-14	416	-9
BL31400	52	-9	208	1	416	-13
BL31428	52	-11	208	-16	416	-10
BL31375	52	-6	208	2	416	-7
BL31393	52	-14	208	1	416	3
BL31419	52	-2	208	-4	416	4
BL31473	52	-4	208	2	416	8
BL31482	52	-7	208	6	416	9
BL31491	52	-14	208	30	416	22
BL31508	52	17	208	38	416	32
BL31517	52	2	208	28	416	24
BL31526	52	4	208	12	416	22
BL31535	52	14	208	1	416	30
BL31544	52	-5	208	15	416	8
BL22232	1	-30	4	5	16	NDN
BL18827	52	4	104	7	208	32
BL26105	52	-5	208	3	NDNDN	NDN
BL26034	52	22	208	48	NDNDN	NDN
BL26114	52	4	208	19	NDNDN	NDN
BL26052	52	3	208	-3	NDNDN	NDN
BL26123	52	12	208	22	NDNDN	NDN

TABLE II. (Continued)

BL26070	52	- 1	208	33	NDNDN	NDN
BL26098	52	- 3	208	13	NDNDN	NDN
BL26043	52	- 2	208	- 6	NDNDN	NDN
BL26061	52	- 2	208	11	NDNDN	NDN
BL26089	52	- 11	208	4	NDNDN	NDN
BL26132	52	- 6	208	- 15	NDNDN	NDN
BL26141	52	- 5	208	5	NDNDN	NDN
BL26150	52	- 1	208	11	NDNDN	NDN
BL26169	52	20	208	- 24	NDNDN	NDN
BL26178	52	18	208	16	NDNDN	NDN
BL26347	52	- 31	208	- 15	NDNDN	NDN
BL26187	52	- 9	208	1	NDNDN	NDN
BL26356	52	- 4	208	- 3	NDNDN	NDN
BL26203	52	- 15	208	43	NDNDN	NDN
BL26294	52	- 64	208	- 11	NDNDN	NDN
BL26221	52	- 17	208	- 1	NDNDN	NDN
BL26301	52	- 36	208	11	NDNDN	NDN
BL26249	52	24	208	- 41	NDNDN	NDN
BL26276	52	- 13	208	3	NDNDN	NDN
BL26285	52	- 79	208	- 11	NDNDN	NDN
BL26230	52	37	208	- 33	NDNDN	NDN
BL26267	52	- 69	208	- 17	NDNDN	NDN
BL26310	52	- 10	208	5	NDNDN	NDN
BL26329	52	- 44	208	10	NDNDN	NDN
BL26338	52	- 43	208	- 3	NDNDN	NDN
BL26196	52	- 43	208	- 25	NDNDN	NDN
BL26212	52	- 29	208	4	NDNDN	NDN
BL26436	52	7	208	- 22	NDNDN	NDN
BL26365	52	- 2	208	17	NDNDN	NDN
BL26427	52	- 7	208	- 15	NDNDN	NDN
BL26383	52	1	208	- 17	NDNDN	NDN
BL26409	52	- 9	208	- 15	NDNDN	NDN
BL26418	52	- 7	208	25	NDNDN	NDN
BL26374	52	- 31	208	32	NDNDN	NDN
BL26392	52	- 2	208	14	NDNDN	NDN
BL26445	52	- 7	208	- 4	NDNDN	NDN
BL26454	52	- 1	208	- 13	NDNDN	NDN
BL26534	52	2	208	4	NDNDN	NDN
BL26463	52	- 37	208	- 9	NDNDN	NDN
BL26543	52	- 14	208	- 48	NDNDN	NDN
BL26481	52	- 11	208	3	NDNDN	NDN
BL26552	52	- 1	208	34	NDNDN	NDN
BL26570	52	- 32	208	3	NDNDN	NDN
BL26525	52	- 12	208	3	NDNDN	NDN
BL26472	52	- 11	208	22	NDNDN	NDN
BL26490	52	- 9	208	- 9	NDNDN	NDN
BL26507	52	- 16	208	- 18	NDNDN	NDN
BL26561	52	- 8	208	17	NDNDN	NDN
BL26516	52	- 6	208	- 5	NDNDN	NDN
BL26589	52	10	208	18	NDNDN	NDN

TABLE II. (Continued)

BL26598	52	12	208	5	NDNDN	NDN
BL26605	52	5	208	28	NDNDN	NDN
BL26614	52	14	208	35	NDNDN	NDN
BL26927	52	0	208	8	NDNDN	NDN
BL26623	52	5	208	20	NDNDN	NDN
BL26696	52	5	208	7	NDNDN	NDN
BL26641	52	3	208	11	NDNDN	NDN
BL26712	52	5	208	0	NDNDN	NDN
BL26650	52	- 8	208	12	NDNDN	NDN
BL26678	52	12	208	4	NDNDN	NDN
BL26632	52	15	208	19	NDNDN	NDN
BL26721	52	16	208	10	NDNDN	NDN
BL26730	52	1	208	- 9	NDNDN	NDN
BL26669	52	- 1	208	10	NDNDN	NDN
BL26687	52	4	208	3	NDNDN	NDN
BL26703	52	4	208	8	NDNDN	NDN
BL26936	52	10	208	8	NDNDN	NDN
BL26945	52	4	208	13	NDNDN	NDN
BL26963	52	5	208	9	NDNDN	NDN
BL26972	52	- 8	208	- 3	NDNDN	NDN
BL26981	52	1	208	- 5	NDNDN	NDN
BL27148	52	- 26	208	9	NDNDN	NDN
BL26990	52	8	208	20	NDNDN	NDN
BL27157	52	3	208	0	NDNDN	NDN
BL27013	52	2	208	5	NDNDN	NDN
BL27166	52	- 32	208	4	NDNDN	NDN
BL27031	52	- 7	208	11	NDNDN	NDN
BL27175	52	5	208	14	NDNDN	NDN
BL27059	208	13	526	5	NDNDN	NDN
BL27077	52	4	208	24	NDNDN	NDN
BL27095	52	13	208	7	NDNDN	NDN
BL27022	52	- 3	208	- 6	NDNDN	NDN
BL27120	52	2	208	7	NDNDN	NDN
BL27086	52	8	208	3	NDNDN	NDN
BL27139	52	8	208	6	NDNDN	NDN
BL27040	52	- 1	208	- 4	NDNDN	NDN
BL27111	52	4	208	22	NDNDN	NDN
BL27068	52	- 7	208	- 5	NDNDN	NDN
BL27102	52	0	208	0	NDNDN	NDN
BL27004	52	- 5	208	4	NDNDN	NDN
BL27184	52	- 1	208	3	NDNDN	NDN
BL27219	52	- 3	208	15	NDNDN	NDN
BL27237	52	- 20	208	- 6	NDNDN	NDN
BL27193	52	- 2	208	23	NDNDN	NDN
BL27228	52	- 10	208	- 2	NDNDN	NDN
BL27200	52	- 2	208	- 7	NDNDN	NDN
BL27246	52	- 12	208	- 24	NDNDN	NDN
BL27255	52	- 4	208	- 14	NDNDN	NDN
BL27264	52	- 28	208	5	NDNDN	NDN
BL27273	52	- 3	208	- 9	NDNDN	NDN

TABLE II. (Continued)

BL27282	52	2	208	-10	NDNDN	NDN
BL27317	52	4	208	-2	NDNDN	NDN
BL27362	52	-8	208	-6	NDNDN	NDN
BL27335	52	-4	208	-2	NDNDN	NDN
BL27308	52	-8	208	-13	NDNDN	NDN
BL27399	52	-3	208	-16	NDNDN	NDN
BL27326	52	-6	208	2	NDNDN	NDN
BL27291	52	-8	208	-20	NDNDN	NDN
BL27371	52	-17	208	-2	NDNDN	NDN
BL27380	52	-21	208	-5	NDNDN	NDN
BL27344	52	-9	208	6	NDNDN	NDN
BL27406	52	-7	208	-13	NDNDN	NDN
BL27415	52	17	208	17	NDNDN	NDN
BL27424	52	19	208	22	NDNDN	NDN
BL27433	52	1	208	13	NDNDN	NDN
BL27513	52	-1	208	31	NDNDN	NDN
BL27442	52	-20	208	-4	NDNDN	NDN
BL27497	52	-13	208	-2	NDNDN	NDN
BL27522	52	-2	208	2	NDNDN	NDN
BL27540	52	-7	208	15	NDNDN	NDN
BL27531	52	13	208	-5	NDNDN	NDN
BL27559	52	8	208	21	NDNDN	NDN
BL27504	52	-4	208	35	NDNDN	NDN
BL27479	52	2	208	11	NDNDN	NDN
BL27460	52	-10	208	-20	NDNDN	NDN
BL27488	52	7	208	NDN	NDNDN	NDN
BL27451	52	-3	208	-8	NDNDN	NDN
BL27568	52	-13	208	24	NDNDN	NDN
BL27577	52	-18	208	11	NDNDN	NDN
BL27586	52	0	208	24	NDNDN	NDN
BL27595	52	-1	208	12	NDNDN	NDN
BL27602	52	0	208	13	NDNDN	NDN
BL27764	52	15	208	24	NDNDN	NDN
BL27773	52	-27	208	1	NDNDN	NDN
BL27620	52	10	208	-8	NDNDN	NDN
BL27782	52	12	208	40	NDNDN	NDN
BL27657	52	3	208	26	NDNDN	NDN
BL27791	52	-14	208	16	NDNDN	NDN
BL27675	52	12	208	14	NDNDN	NDN
BL27808	52	10	208	24	NDNDN	NDN
BL27693	52	-16	208	26	NDNDN	NDN
BL27755	52	0	208	6	NDNDN	NDN
BL27728	52	-8	208	18	NDNDN	NDN
BL27737	52	30	208	36	NDNDN	NDN
BL27746	52	-5	208	-18	NDNDN	NDN
BL27719	52	6	208	16	NDNDN	NDN
BL27611	52	1	208	26	NDNDN	NDN
BL27648	52	9	208	19	NDNDN	NDN
BL27684	52	-3	208	32	NDNDN	NDN
BL27700	52	10	208	2	NDNDN	NDN

TABLE II. (Continued)

BL27817	52	22	208	47	NDNDN	NDN
BL27951	52	8	208	11	NDNDN	NDN
BL27835	52	14	208	28	NDNDN	NDN
BL27844	52	- 3	208	19	NDNDN	NDN
BL27899	52	9	208	34	NDNDN	NDN
BL27826	52	17	208	39	NDNDN	NDN
BL27960	52	0	208	20	NDNDN	NDN
BL27979	52	20	208	40	NDNDN	NDN
BL27988	52	- 20	208	41	NDNDN	NDN
BL27997	52	- 2	208	13	NDNDN	NDN
BL28181	52	- 12	208	- 2	NDNDN	NDN
BL28001	52	22	208	26	NDNDN	NDN
BL28190	52	0	208	29	NDNDN	NDN
BL28136	52	2	208	2	NDNDN	NDN
BL28154	52	5	208	10	NDNDN	NDN
BL28163	52	13	208	0	NDNDN	NDN
BL28172	52	5	208	2	NDNDN	NDN
BL28010	52	- 2	208	30	NDNDN	NDN
BL28145	52	5	208	9	NDNDN	NDN
BL28207	52	8	208	33	NDNDN	NDN
BL28216	52	- 10	208	17	NDNDN	NDN
BL28225	52	4	208	15	NDNDN	NDN
BL28234	52	1	208	29	NDNDN	NDN
BL28243	52	13	208	23	NDNDN	NDN
BL28252	52	- 2	208	21	NDNDN	NDN
BL28387	52	3	208	21	NDNDN	NDN
BL28261	52	7	208	9	NDNDN	NDN
BL28396	52	- 1	208	27	NDNDN	NDN
BL28412	52	16	208	27	NDNDN	NDN
BL28289	52	11	208	27	NDNDN	NDN
BL28421	52	15	208	32	NDNDN	NDN
BL28305	52	8	208	25	NDNDN	NDN
BL28430	52	- 6	208	13	NDNDN	NDN
BL28270	52	38	208	47	NDNDN	NDN
BL28369	52	- 13	208	13	NDNDN	NDN
BL28403	52	4	208	28	NDNDN	NDN
BL28298	52	2	208	28	NDNDN	NDN
BL23337	52	14	208	31	NDNDN	NDN
BL31973	52	5	208	34	NDNDN	NDN
BL31982	52	4	208	4	NDNDN	NDN
BL32149	52	- 2	208	9	NDNDN	NDN
BL32158	52	3	208	- 3	NDNDN	NDN
BL32005	52	- 6	208	- 3	NDNDN	NDN
BL32087	52	3	208	- 7	NDNDN	NDN
BL32167	52	NDN	208	NDN	NDNDN	NDN
BL32103	52	3	208	4	NDNDN	NDN
BL32176	52	5	208	- 13	NDNDN	NDN
BL32121	52	- 12	208	17	NDNDN	NDN
BL32185	52	- 14	208	- 2	NDNDN	NDN
BL31991	52	- 11	208	- 8	NDNDN	NDN

TABLE II. (Continued)

BL32014	52	- 3	208	- 1	NDNDN	NDN
BL32096	52	- 7	208	- 11	NDNDN	NDN
BL32112	52	- 19	208	NDN	NDNDN	NDN
BL32130	52	- 13	208	- 16	NDNDN	NDN
BL32194	52	- 15	208	- 19	NDNDN	NDN
BL32201	52	- 15	208	4	NDNDN	NDN
BL32041	52	- 17	208	- 5	NDNDN	NDN
BL32069	52	- 2	208	11	NDNDN	NDN
BL32023	52	- 22	208	- 6	NDNDN	NDN
BL32050	52	10	208	NDN	NDNDN	NDN
BL32078	52	- 5	208	- 4	NDNDN	NDN
BL32210	52	5	208	30	NDNDN	NDN
BL32283	52	- 3	208	14	NDNDN	NDN
BL32238	52	2	208	13	NDNDN	NDN
BL32256	52	- 3	208	29	NDNDN	NDN
BL32265	52	- 19	208	5	NDNDN	NDN
BL32229	52	3	208	11	NDNDN	NDN
BL32247	52	- 5	208	8	NDNDN	NDN
BL32514	52	12	208	14	NDNDN	NDN
BL32345	52	- 17	208	27	NDNDN	NDN
BL32523	52	- 6	208	34	NDNDN	NDN
BL32461	52	- 3	208	31	NDNDN	NDN
BL32532	52	- 8	208	28	NDNDN	NDN
BL32569	52	- 5	208	17	NDNDN	NDN
BL32489	52	0	208	15	NDNDN	NDN
BL32578	52	2	208	31	NDNDN	NDN
BL32443	52	- 2	208	15	NDNDN	NDN
BL32498	52	16	208	49	NDNDN	NDN
BL32541	52	- 6	208	27	NDNDN	NDN
BL32505	52	5	208	10	NDNDN	NDN
BL32470	52	- 5	208	24	NDNDN	NDN
BL32587	52	1	208	37	NDNDN	NDN
BL32667	52	8	208	32	NDNDN	NDN
BL32596	52	- 7	208	36	NDNDN	NDN
BL32676	52	- 6	208	7	NDNDN	NDN
BL32612	52	- 7	208	33	NDNDN	NDN
BL32685	52	- 41	208	11	NDNDN	NDN
BL32630	52	- 33	208	- 8	NDNDN	NDN
BL32729	52	16	208	28	NDNDN	NDN
BL32658	52	- 28	208	3	NDNDN	NDN
BL32738	52	- 32	208	11	NDNDN	NDN
BL32621	52	2	208	34	NDNDN	NDN
BL32747	52	12	208	9	NDNDN	NDN
BL32694	52	5	208	44	NDNDN	NDN
BL32710	52	2	208	32	NDNDN	NDN
BL32603	52	0	208	12	NDNDN	NDN
BL32649	52	- 4	208	- 3	NDNDN	NDN
BL32701	52	- 25	208	12	NDNDN	NDN
BL32756	52	- 19	208	15	NDNDN	NDN
BL32765	52	0	208	29	NDNDN	NDN

TABLE II. (Continued)

BL32774	52	15	208	5	NDNDN NDN
BL32783	52	1	208	6	NDNDN NDN
BL32792	52	2	208	- 9	NDNDN NDN
BL32809	52	- 10	208	18	NDNDN NDN
BL32961	52	6	208	16	NDNDN NDN
BL32818	52	- 2	208	4	NDNDN NDN
BL32890	52	8	208	- 3	NDNDN NDN
BL32907	52	19	208	3	NDNDN NDN
BL32845	52	15	208	- 8	NDNDN NDN
BL32916	52	21	208	8	NDNDN NDN
BL32863	52	15	208	39	NDNDN NDN
BL32881	52	9	208	12	NDNDN NDN
BL32836	52	7	208	20	NDNDN NDN
BL32854	52	- 10	208	10	NDNDN NDN
BL32872	52	5	208	3	NDNDN NDN
BL32925	52	14	208	11	NDNDN NDN
BL32934	52	13	208	19	NDNDN NDN
BL32943	52	17	208	11	NDNDN NDN
BL32952	52	15	208	5	NDNDN NDN
BL32827	52	20	208	10	NDNDN NDN
BL52669	52	16	416	33	NDNDN NDN
BL33235	52	- 17	208	2	NDNDN NDN
BL33244	52	5	208	7	NDNDN NDN
BL32452	52	3	208	0	NDNDN NDN
BL33253	52	- 11	208	16	NDNDN NDN
BL33208	52	7	208	8	NDNDN NDN
BL33226	52	- 13	208	18	NDNDN NDN
BL52678	52	14	416	28	NDNDN NDN
BL33191	52	- 5	208	8	NDNDN NDN
BL33217	52	5	208	17	NDNDN NDN
BL33262	52	1	208	5	NDNDN NDN
BL33271	52	- 3	208	8	NDNDN NDN
BL33280	52	- 6	208	4	NDNDN NDN
BL33299	52	- 3	208	24	NDNDN NDN
BL33306	52	- 11	208	21	NDNDN NDN
BL33315	52	- 2	208	4	NDNDN NDN
BL33422	52	- 9	208	- 4	NDNDN NDN
BL33324	52	- 6	208	4	NDNDN NDN
BL33440	52	- 13	208	9	NDNDN NDN
BL33342	52	- 4	208	11	NDNDN NDN
BL33495	52	- 15	208	12	NDNDN NDN
BL33360	52	- 29	208	5	NDNDN NDN
BL33502	52	- 6	208	10	NDNDN NDN
BL33388	52	18	208	30	NDNDN NDN
BL33511	52	- 11	208	0	NDNDN NDN
BL33397	52	- 19	208	4	NDNDN NDN
BL33404	52	0	208	1	NDNDN NDN
BL33486	52	11	208	21	NDNDN NDN
BL33431	52	- 24	208	- 6	NDNDN NDN
BL33459	52	- 2	208	7	NDNDN NDN

TABLE II. (Continued)

BL33413	52	- 20	208	4	NDNDN	NDN
BL33333	52	20	208	- 6	NDNDN	NDN
BL33351	52	2	208	23	NDNDN	NDN
BL33379	52	5	208	11	NDNDN	NDN
BL33468	52	- 12	208	26	NDNDN	NDN
BL33477	52	- 3	208	13	NDNDN	NDN
BL52203	52	- 16	208	- 13	832	- 16
BL33557	52	2	208	- 11	NDNDN	NDN
BL33691	52	5	208	- 19	NDNDN	NDN
BL33539	52	- 4	208	16	NDNDN	NDN
BL33708	52	5	208	9	NDNDN	NDN
BL33520	52	- 5	208	21	NDNDN	NDN
BL33717	52	6	208	13	NDNDN	NDN
BL33575	52	31	208	NDN	NDNDN	NDN
BL33726	52	- 3	208	5	NDNDN	NDN
BL33593	52	2	208	- 2	NDNDN	NDN
BL33673	52	5	208	4	NDNDN	NDN
BL33619	52	- 24	208	- 22	NDNDN	NDN
BL33584	52	13	208	12	NDNDN	NDN
BL33646	52	- 1	208	- 10	NDNDN	NDN
BL33600	52	- 8	208	15	NDNDN	NDN
BL33664	52	- 7	208	- 1	NDNDN	NDN
BL33682	52	- 1	208	- 20	NDNDN	NDN
BL33548	52	6	208	2	NDNDN	NDN
BL33566	52	8	208	- 2	NDNDN	NDN
BL33655	52	9	208	16	NDNDN	NDN
BL33637	52	- 10	208	12	NDNDN	NDN
BL33780	52	7	208	2	NDNDN	NDN
BL33753	52	14	208	19	NDNDN	NDN
BL33762	52	0	208	12	NDNDN	NDN
BL33771	52	- 2	208	7	NDNDN	NDN
BL33744	52	6	208	- 1	NDNDN	NDN
BL33799	52	- 4	208	16	NDNDN	NDN
BL33806	52	11	208	12	NDNDN	NDN
BL33815	52	- 5	208	4	NDNDN	NDN
BL33824	52	1	208	18	NDNDN	NDN
BL33977	52	- 1	208	- 7	NDNDN	NDN
BL33986	52	2	208	21	NDNDN	NDN
BL33842	52	- 16	208	- 12	NDNDN	NDN
BL33995	52	- 1	208	11	NDNDN	NDN
BL33860	52	6	208	12	NDNDN	NDN
BL34009	52	4	208	0	NDNDN	NDN
BL33888	52	1	208	4	NDNDN	NDN
BL34018	52	5	208	10	NDNDN	NDN
BL33904	52	9	208	18	NDNDN	NDN
BL34027	52	2	208	12	NDNDN	NDN
BL33922	52	- 1	208	8	NDNDN	NDN
BL34036	52	10	208	- 1	NDNDN	NDN
BL33940	52	5	208	7	NDNDN	NDN
BL33959	52	3	208	8	NDNDN	NDN

TABLE II. (Continued)

BL34045	52	- 10	208	NDN	NDNDN	NDN
BL33833	52	6	208	4	NDNDN	NDN
BL34054	52	2	208	- 5	NDNDN	NDN
BL33879	52	5	208	0	NDNDN	NDN
BL33897	52	34	208	31	NDNDN	NDN
BL33931	52	0	208	6	NDNDN	NDN
BL33968	52	13	208	17	NDNDN	NDN
BL33851	52	5	208	7	NDNDN	NDN
BL33913	52	- 1	208	11	NDNDN	NDN
BL34063	52	6	208	- 20	NDNDN	NDN
BL34072	52	- 26	208	- 17	NDNDN	NDN
BL34081	52	- 50	208	- 14	NDNDN	NDN
BL34090	52	- 18	208	- 30	NDNDN	NDN
BL34107	52	- 9	208	- 24	NDNDN	NDN
BL34321	52	- 16	208	- 24	NDNDN	NDN
BL34410	52	- 37	208	10	NDNDN	NDN
BL34330	52	- 33	208	- 35	NDNDN	NDN
BL34358	52	- 21	208	- 3	NDNDN	NDN
BL34349	52	2	208	- 8	NDNDN	NDN
BL34385	52	- 15	208	- 5	NDNDN	NDN
BL34376	52	- 4	208	- 12	NDNDN	NDN
BL34401	52	- 3	208	- 14	NDNDN	NDN
BL34429	52	- 24	208	11	NDNDN	NDN
BL34438	52	0	208	8	NDNDN	NDN
BL34394	52	- 28	208	- 13	NDNDN	NDN
BL34447	52	- 5	208	15	NDNDN	NDN
BL34456	52	- 10	208	25	NDNDN	NDN
BL34465	52	10	208	37	NDNDN	NDN
BL34483	52	- 7	208	15	NDNDN	NDN
BL34492	52	10	208	23	NDNDN	NDN
BL34643	52	17	208	30	NDNDN	NDN
BL34652	52	31	208	23	NDNDN	NDN
BL34581	52	31	208	36	NDNDN	NDN
BL34545	52	13	208	40	NDNDN	NDN
BL34590	52	10	208	23	NDNDN	NDN
BL34563	52	6	208	11	NDNDN	NDN
BL34607	52	- 6	208	26	NDNDN	NDN
BL34572	52	0	208	19	NDNDN	NDN
BL34527	52	- 9	208	24	NDNDN	NDN
BL34536	52	1	208	19	NDNDN	NDN
BL34554	52	9	208	13	NDNDN	NDN
BL34616	52	11	208	26	NDNDN	NDN
BL34625	52	10	208	20	NDNDN	NDN
BL34634	52	0	208	17	NDNDN	NDN
BL34509	52	1	208	13	NDNDN	NDN
BL34518	52	4	208	9	NDNDN	NDN
BL34867	52	- 7	208	1	NDNDN	NDN
BL34732	52	- 4	208	18	NDNDN	NDN
BL34661	52	11	208	16	NDNDN	NDN
BL34910	52	- 6	208	11	NDNDN	NDN

TABLE II. (Continued)

BL34698	52	- 5	208	0	NDNDN	NDN
BL34714	52	- 6	208	9	NDNDN	NDN
BL34894	52	1	208	17	NDNDN	NDN
BL34876	52	12	208	42	NDNDN	NDN
BL34885	52	1	208	13	NDNDN	NDN
BL34787	52	- 18	208	14	NDNDN	NDN
BL34938	52	7	208	50	NDNDN	NDN
BL34812	52	- 13	208	25	NDNDN	NDN
BL34830	52	- 10	208	- 6	NDNDN	NDN
BL34849	52	4	208	21	NDNDN	NDN
BL34858	52	- 17	208	3	NDNDN	NDN
BL34689	52	3	208	25	NDNDN	NDN
BL34705	52	- 9	208	- 6	NDNDN	NDN
BL34723	52	- 3	208	33	NDNDN	NDN
BL34778	52	- 4	208	- 4	NDNDN	NDN
BL34796	52	- 18	208	- 4	NDNDN	NDN
BL34821	52	- 5	208	NDN	NDNDN	NDN
BC29446	52	26	208	26	NDNDN	NDN
BL12914	52	30	208	26	NDNDN	NDN
ZF25638	52	26	208	38	NDNDN	NDN
BL34947	52	19	208	28	NDNDN	NDN
BL34956	52	6	208	18	NDNDN	NDN
BL34965	52	28	208	17	NDNDN	NDN
BL34974	52	19	208	18	NDNDN	NDN
BL35355	52	21	208	48	NDNDN	NDN
AT56097	52	19	208	37	NDNDN	NDN
BL34670	52	7	208	28	NDNDN	NDN
BL34750	52	13	208	29	NDNDN	NDN
BL35006	52	16	208	22	NDNDN	NDN
BL34803	52	23	208	31	NDNDN	NDN
BL35015	52	11	208	13	NDNDN	NDN
BL34929	52	41	208	50	NDNDN	NDN
BL35024	52	4	208	15	NDNDN	NDN
BL34992	52	24	208	19	NDNDN	NDN
BL34741	52	18	208	33	NDNDN	NDN
BL34769	52	34	208	32	NDNDN	NDN
BL34901	52	2	208	27	NDNDN	NDN
BL35033	52	16	208	44	NDNDN	NDN
BL35042	52	2	208	13	NDNDN	NDN
BL52132	52	- 12	208	3	624	18
AD55689	52	9	208	24	NDNDN	NDN
BL35079	52	- 7	208	6	NDNDN	NDN
BL35168	52	- 6	208	15	NDNDN	NDN
AD56855	52	15	208	12	NDNDN	NDN
BL35177	52	11	208	20	NDNDN	NDN
BK74393	52	0	208	11	NDNDN	NDN
BL35186	52	3	208	29	NDNDN	NDN
BL35122	52	6	208	35	NDNDN	NDN
BL35131	52	- 4	208	32	NDNDN	NDN
BK98811	52	- 1	208	10	NDNDN	NDN

TABLE II. (Continued)

BL35104	52	5	208	23	NDNDN	NDN
BL35113	52	2	208	14	NDNDN	NDN
BK70288	52	- 1	208	9	NDNDN	NDN
BL35051	52	10	208	17	NDNDN	NDN
BL35140	52	6	208	21	NDNDN	NDN
BL35159	52	- 4	208	17	NDNDN	NDN
BL35088	52	14	208	38	NDNDN	NDN
BL35097	52	- 10	208	11	NDNDN	NDN
BL35060	52	6	208	10	NDNDN	NDN
BL54083	52	1	416	7	NDNDN	NDN
BL35248	52	13	208	25	NDNDN	NDN
BL35257	52	- 16	208	- 9	NDNDN	NDN
BL35202	52	- 6	208	- 22	NDNDN	NDN
BL35220	52	0	208	- 6	NDNDN	NDN
BL35239	52	- 8	208	- 8	NDNDN	NDN
BL35195	52	3	208	14	NDNDN	NDN
BL35211	52	- 12	208	6	NDNDN	NDN
BL35266	52	- 14	208	- 4	NDNDN	NDN
BL35275	52	- 18	208	- 4	NDNDN	NDN
BL35284	208	2	NDNDN	NDN	NDNDN	NDN
BL37402	52	20	208	36	NDNDN	NDN
BL37420	52	12	208	41	NDNDN	NDN
BL37448	52	5	208	28	NDNDN	NDN
BL37457	52	23	208	43	NDNDN	NDN
BL37377	52	24	208	28	NDNDN	NDN
BL37475	52	9	208	23	NDNDN	NDN
BL37386	52	13	208	18	NDNDN	NDN
BL37439	52	12	208	35	NDNDN	NDN
BL37395	52	16	208	42	NDNDN	NDN
BL37484	52	20	208	34	NDNDN	NDN
BL37493	52	17	208	28	NDNDN	NDN
BL37500	52	3	208	15	NDNDN	NDN
BL37528	52	14	208	27	NDNDN	NDN
BL36478	52	12	208	19	NDNDN	NDN
BL36487	52	- 16	208	17	NDNDN	NDN
BL36576	52	9	208	35	NDNDN	NDN
BL36503	52	35	208	NDN	NDNDN	NDN
BL36585	52	- 1	208	14	NDNDN	NDN
BL36521	52	- 12	208	15	NDNDN	NDN
BL36594	52	3	208	2	NDNDN	NDN
BL36549	52	- 10	208	- 1	NDNDN	NDN
BL36567	52	5	208	25	NDNDN	NDN
BL36512	52	- 13	208	- 9	NDNDN	NDN
BL36530	52	10	208	- 6	NDNDN	NDN
BL36558	52	10	208	12	NDNDN	NDN
BL36601	52	- 2	208	25	NDNDN	NDN
BL36610	52	11	208	9	NDNDN	NDN
BL36629	52	4	208	0	NDNDN	NDN
BL36638	52	15	208	NDN	NDNDN	NDN
BL36647	52	10	208	40	NDNDN	NDN

TABLE II. (Continued)

BL36656	52	-1	208	6	NDNDN	NDN
BL36665	52	16	208	11	NDNDN	NDN
BL36674	52	11	208	NDN	NDNDN	NDN
BL36683	52	-33	208	-13	NDNDN	NDN
BL36692	52	-21	208	-21	NDNDN	NDN
BL36709	52	-30	208	-17	NDNDN	NDN
BL36718	52	-12	208	-8	NDNDN	NDN
BL36727	52	-43	208	-36	NDNDN	NDN
BL36736	52	-6	208	8	NDNDN	NDN
BL36745	52	-21	208	-16	NDNDN	NDN
BL36754	52	-32	208	-26	NDNDN	NDN
BL36763	52	-36	208	-8	NDNDN	NDN
BL36843	52	-23	208	-28	NDNDN	NDN
BL36772	52	-41	208	-33	NDNDN	NDN
BL36852	52	-23	208	-4	NDNDN	NDN
BL36790	52	38	208	NDN	NDNDN	NDN
BL36861	52	-9	208	-16	NDNDN	NDN
BL36816	52	-40	208	-20	NDNDN	NDN
BL36834	52	-42	208	-54	NDNDN	NDN
BL36781	52	-28	208	-5	NDNDN	NDN
BL36807	52	-11	208	4	NDNDN	NDN
BL36825	52	-44	208	0	NDNDN	NDN
BL36870	52	1	208	19	NDNDN	NDN
BL36898	52	-24	208	-7	NDNDN	NDN
BL36905	52	-6	208	20	NDNDN	NDN
BL36914	52	-15	208	4	NDNDN	NDN
BL36923	52	10	208	0	NDNDN	NDN
BL36941	52	-2	208	6	NDNDN	NDN
BL36950	52	9	208	22	NDNDN	NDN
BL36969	52	-35	208	-9	NDNDN	NDN
BL36978	52	1	208	16	NDNDN	NDN
BL36987	52	-7	208	-11	NDNDN	NDN
BL36996	52	2	208	8	NDNDN	NDN
BL37073	52	22	208	38	NDNDN	NDN
BL37000	52	11	208	8	NDNDN	NDN
BL37082	52	4	208	30	NDNDN	NDN
BL37028	52	2	208	14	NDNDN	NDN
BL37091	52	-1	208	14	NDNDN	NDN
BL37046	52	-6	208	12	NDNDN	NDN
BL37064	52	5	208	2	NDNDN	NDN
BL37019	52	0	208	15	NDNDN	NDN
BL37037	52	5	208	-8	NDNDN	NDN
BL37055	52	6	208	16	NDNDN	NDN
BL37108	52	-3	208	39	NDNDN	NDN
BL37117	52	-3	208	4	NDNDN	NDN
BL37126	52	2	208	13	NDNDN	NDN
BL37144	52	18	208	8	NDNDN	NDN
BL37153	52	12	208	7	NDNDN	NDN
BL37162	52	15	208	39	NDNDN	NDN
BL37171	52	17	208	18	NDNDN	NDN

TABLE II. (Continued)

BL37742	52		16	416		46	NDNDN	NDN
BL37797	52		19	416		26	NDNDN	NDN
BL37822	52		18	416		28	NDNDN	NDN
BL37895	52		18	416		34	NDNDN	NDN
BL37902	52		30	416		32	NDNDN	NDN
BL37331	52		9	208		2	NDNDN	NDN
BL37911	52	-	9	416	-	12	NDNDN	NDN
BL37368	52	-	13	208	-	8	NDNDN	NDN
BL38034	52	-	10	416		18	NDNDN	NDN
BL37411	52	-	13	208		0	NDNDN	NDN
BL37251	52	-	5	208	-	5	NDNDN	NDN
BL37297	52		1	208		8	NDNDN	NDN
BL37975	52	-	20	416	-	3	NDNDN	NDN
BL37215	52	-	5	208	-	1	NDNDN	NDN
BL38285	52	-	14	208	-	5	NDNDN	NDN
BL37279	52	-	16	208		2	NDNDN	NDN
BL38301	52	-	12	208		12	NDNDN	NDN
BL38230	52	-	14	208		16	NDNDN	NDN
BL38310	52	-	6	208		6	NDNDN	NDN
BL38258	52	-	6	208		15	NDNDN	NDN
BL38276	52	-	13	208		6	NDNDN	NDN
BL38221	52	-	25	208	-	24	NDNDN	NDN
BL38249	52	-	16	208		3	NDNDN	NDN
BL38267	52	-	10	208		12	NDNDN	NDN
BL38329	52	-	11	208		7	NDNDN	NDN
BL38338	52		1	208		8	NDNDN	NDN
BL39942	52		9	416		25	NDNDN	NDN
BL39951	52		1	416		16	NDNDN	NDN
BL39960	52		18	416		23	NDNDN	NDN
BL39988	52		26	416		20	NDNDN	NDN
BL38365	52		16	208		40	NDNDN	NDN
BL39997	52		8	416		20	NDNDN	NDN
BL38445	52		15	208		19	NDNDN	NDN
BL52838	52		16	416		30	NDNDN	NDN
BL38383	52		7	208		42	NDNDN	NDN
BL38427	52		9	208		32	NDNDN	NDN
BL38436	52		18	208		26	NDNDN	NDN
AE80043	52		11	416		24	NDNDN	NDN
BL52829	52		11	416		19	NDNDN	NDN
BL38347	52		28	208		43	NDNDN	NDN
BL38418	52		18	208		38	NDNDN	NDN
BL38356	52		20	208		18	NDNDN	NDN
BL38374	52		2	208		16	NDNDN	NDN
BL38392	52		33	208		42	NDNDN	NDN
BL38454	52		11	208		34	NDNDN	NDN
BL38463	52		3	208		15	NDNDN	NDN
BL38472	52		18	208		28	NDNDN	NDN
BL38481	52		25	208		32	NDNDN	NDN
BL38490	52		18	208		21	NDNDN	NDN
BL38669	52		6	208		14	NDNDN	NDN

TABLE II. (Continued)

BL38507	52	4	208	17	NDNDN	NDN
BL38687	52	18	208	27	NDNDN	NDN
BL38525	52	12	208	14	NDNDN	NDN
BL38696	52	18	208	33	NDNDN	NDN
BL38543	52	-5	208	11	NDNDN	NDN
BL38703	52	13	208	26	NDNDN	NDN
BL38561	52	2	208	23	NDNDN	NDN
BL38712	52	5	208	32	NDNDN	NDN
BL38589	52	19	208	50	NDNDN	NDN
BL38721	52	13	208	32	NDNDN	NDN
BL38605	52	11	208	26	NDNDN	NDN
BL38623	52	15	208	25	NDNDN	NDN
BL38614	52	-1	208	0	NDNDN	NDN
BL38632	52	4	208	13	NDNDN	NDN
BL38516	52	-11	208	6	NDNDN	NDN
BL38534	52	1	208	12	NDNDN	NDN
BL38552	52	-2	208	39	NDNDN	NDN
BL38570	52	2	208	14	NDNDN	NDN
BL38598	52	3	208	35	NDNDN	NDN
BL38641	52	20	208	27	NDNDN	NDN
BL55400	52	11	208	34	NDNDN	NDN
BL38749	52	-6	208	9	NDNDN	NDN
BL38758	52	4	208	5	NDNDN	NDN
BL38767	52	3	208	27	NDNDN	NDN
BL38776	52	6	208	20	NDNDN	NDN
BL38785	52	8	208	10	NDNDN	NDN
BL38794	52	-7	208	16	NDNDN	NDN
BL38909	52	1	208	18	NDNDN	NDN
BL38990	52	1	208	10	NDNDN	NDN
BL38829	52	22	208	23	NDNDN	NDN
BL38945	52	2	208	3	NDNDN	NDN
BL38972	52	-1	208	-10	NDNDN	NDN
BL38981	52	-6	208	1	NDNDN	NDN
BL38810	52	5	208	4	NDNDN	NDN
BL38838	52	-6	208	-2	NDNDN	NDN
BL38865	52	-3	208	25	NDNDN	NDN
BL38963	52	-11	208	-3	NDNDN	NDN
BL38874	52	10	208	26	NDNDN	NDN
BL38927	52	-4	208	15	NDNDN	NDN
BL38954	52	-7	208	4	NDNDN	NDN
BL39004	52	9	208	13	NDNDN	NDN
AB37823	52	5	208	11	NDNDN	NDN
AH72519	52	3	208	25	NDNDN	NDN
AB75181	52	6	208	23	NDNDN	NDN
AJ44252	52	1	208	28	NDNDN	NDN
AE99480	52	8	208	23	NDNDN	NDN
AJ56663	52	20	208	26	NDNDN	NDN
AF34635	52	-4	208	15	NDNDN	NDN
AG64889	52	-3	208	7	NDNDN	NDN
AE39895	52	17	208	18	NDNDN	NDN

TABLE II. (Continued)

AJ56672	52	-1	208	33	NDNDN	NDN
AK89836	52	3	208	19	NDNDN	NDN
AG53260	52	7	208	0	NDNDN	NDN
AH72297	52	8	208	16	NDNDN	NDN
AT00380	52	9	208	18	NDNDN	NDN
AT12219	52	15	208	33	NDNDN	NDN
AV82346	52	30	208	21	NDNDN	NDN
BE11220	52	9	208	15	NDNDN	NDN
BL39013	52	12	208	20	NDNDN	NDN
BE99886	52	6	208	28	NDNDN	NDN
ZB25745	52	9	208	22	NDNDN	NDN
ZC21573	52	8	208	21	NDNDN	NDN
ZC21715	52	16	208	35	NDNDN	NDN
ZN46221	52	14	208	31	NDNDN	NDN
ZN65182	52	5	208	21	NDNDN	NDN
BL11328	52	13	208	17	NDNDN	NDN
AG15706	52	8	208	19	NDNDN	NDN
AG53439	52	-9	208	26	NDNDN	NDN
AG60998	52	-23	208	12	NDNDN	NDN
AG61011	52	10	208	23	NDNDN	NDN
AG61048	52	-12	208	-2	NDNDN	NDN
AG77135	52	1	208	4	NDNDN	NDN
AG77555	52	3	208	-2	NDNDN	NDN
AG84265	52	-29	208	-17	NDNDN	NDN
AG84274	52	-25	208	6	NDNDN	NDN
AG84283	52	-14	208	11	NDNDN	NDN
AH11801	52	-14	208	18	NDNDN	NDN
AH11810	52	-1	208	9	NDNDN	NDN
AH11829	52	-2	208	2	NDNDN	NDN
AH11838	52	0	208	6	NDNDN	NDN
AH11847	52	0	208	16	NDNDN	NDN
AH11856	52	-2	208	7	NDNDN	NDN
AH11865	52	19	208	29	NDNDN	NDN
AH11883	52	17	208	9	NDNDN	NDN
AH11909	52	-2	208	-6	NDNDN	NDN
AH11918	52	13	208	6	NDNDN	NDN
AH11981	52	0	208	28	NDNDN	NDN
AH32284	52	5	208	15	NDNDN	NDN
AH52955	52	28	208	32	NDNDN	NDN
AT83905	52	4	208	16	NDNDN	NDN
AJ07606	52	7	208	18	NDNDN	NDN
AH89149	52	-4	208	4	NDNDN	NDN
AJ07633	52	-4	208	35	NDNDN	NDN
AJ07599	52	2	208	35	NDNDN	NDN
AH89158	52	15	208	28	NDNDN	NDN
AY28212	52	13	208	23	NDNDN	NDN
AL21704	52	0	208	20	NDNDN	NDN
ZA27913	52	8	208	45	NDNDN	NDN
ZB36935	52	16	208	33	NDNDN	NDN
ZB36980	52	14	208	26	NDNDN	NDN

TABLE II. (Continued)

BL39031	52	- 2	208	12	NDNDN	NDN
BL39040	52	25	208	48	NDNDN	NDN
BL39077	52	11	208	29	NDNDN	NDN
ZM38242	52	8	208	19	NDNDN	NDN
BL39086	52	13	208	20	NDNDN	NDN
ZB37049	52	2	208	42	NDNDN	NDN
BL56461	52	7	208	11	NDNDN	NDN
BL39059	52	21	208	32	NDNDN	NDN
BL39022	52	14	208	22	NDNDN	NDN
BL56470	52	7	208	18	NDNDN	NDN
BL39095	52	22	208	19	NDNDN	NDN
BL39102	52	12	208	25	NDNDN	NDN
BL39291	52	29	208	NDN	NDNDN	NDN
BL39111	52	13	208	15	NDNDN	NDN
BL39148	52	8	208	32	NDNDN	NDN
BL39175	52	19	208	30	NDNDN	NDN
BL39184	52	6	208	27	NDNDN	NDN
BL39193	52	7	208	22	NDNDN	NDN
BL39282	52	13	208	17	NDNDN	NDN
BL39139	52	7	208	27	NDNDN	NDN
BL39317	52	- 53	208	- 14	NDNDN	NDN
BL39353	52	- 28	208	- 39	NDNDN	NDN
BL39380	52	- 15	208	- 13	NDNDN	NDN
BL39399	52	- 18	208	- 11	NDNDN	NDN
BL40990	52	- 26	208	9	NDNDN	NDN
BL41317	52	- 22	208	- 14	NDNDN	NDN
BL44390	52	- 4	208	- 2	NDNDN	NDN
BL41415	52	- 4	208	6	NDNDN	NDN
BL44596	52	- 4	208	17	NDNDN	NDN
BL41595	52	- 19	208	- 6	NDNDN	NDN
BL42672	52	- 11	208	18	NDNDN	NDN
BL43642	52	- 20	208	12	NDNDN	NDN
BL43571	52	- 22	208	- 10	NDNDN	NDN
BL41586	52	- 8	208	14	NDNDN	NDN
BL42403	52	1	208	17	NDNDN	NDN
BL05848	0.20	- 21	0.81	11	3.25	27
BL20649	0.20	- 1	0.81	18	3.25	42
BL20649	0.20	- 6	0.81	3	3.25	- 1
BL49993	0.20	- 13	0.81	- 12	3.25	35
BL45468	52	- 12	208	- 10	NDNDN	NDN
BL45495	52	- 13	208	14	NDNDN	NDN
AB22591	52	- 5	208	7	NDNDN	NDN
AB33227	52	- 3	208	- 9	NDNDN	NDN
AB35258	52	1	208	5	NDNDN	NDN
AB75396	52	- 5	208	- 4	NDNDN	NDN
AB45496	52	- 13	208	- 6	NDNDN	NDN
AB75403	52	9	208	5	NDNDN	NDN
AB75216	52	- 17	208	5	NDNDN	NDN
AB75449	52	- 9	208	- 1	NDNDN	NDN
AB75314	52	0	208	- 5	NDNDN	NDN

TABLE II. (Continued)

AB75378	52	4	208	6	NDNDN	NDN
AB75136	52	-15	208	-5	NDNDN	NDN
AB75270	52	-7	208	0	NDNDN	NDN
AB75341	52	-13	208	-12	NDNDN	NDN
AB75458	52	6	208	22	NDNDN	NDN
AB95076	52	21	208	34	NDNDN	NDN
AC73806	52	13	208	27	NDNDN	NDN
AC73815	52	2	208	23	NDNDN	NDN
AD00488	52	17	208	13	NDNDN	NDN
AD21978	52	11	208	16	NDNDN	NDN
AD43947	52	15	208	25	NDNDN	NDN
AD88839	52	16	208	43	NDNDN	NDN
AE46372	52	10	208	27	NDNDN	NDN
AE75604	52	46	208	48	NDNDN	NDN
AE87462	52	29	208	34	NDNDN	NDN
AE88192	52	31	208	22	NDNDN	NDN
AJ85262	52	13	208	19	NDNDN	NDN
AF15854	52	36	208	39	NDNDN	NDN
AJ85422	52	5	208	19	NDNDN	NDN
AJ10550	52	19	208	12	NDNDN	NDN
AJ85655	52	-3	208	7	NDNDN	NDN
AJ60621	52	0	208	14	NDNDN	NDN
AJ76889	52	17	208	31	NDNDN	NDN
AF93170	52	-1	208	13	NDNDN	NDN
AJ48152	52	15	208	16	NDNDN	NDN
AJ67915	52	0	208	44	NDNDN	NDN
AK03489	52	16	208	32	NDNDN	NDN
AK12175	52	7	208	6	NDNDN	NDN
AK34813	52	-17	208	-18	NDNDN	NDN
AK56524	52	-11	208	8	NDNDN	NDN
AK57352	52	7	208	-1	NDNDN	NDN
AF97025	52	7	208	9	NDNDN	NDN
AK96608	52	-19	208	11	NDNDN	NDN
AL04730	52	-12	208	-4	NDNDN	NDN
AL05095	52	-5	208	-4	NDNDN	NDN
AL13980	52	-13	208	14	NDNDN	NDN
BJ85337	52	-12	208	-13	NDNDN	NDN
AF17938	52	-28	208	12	NDNDN	NDN
AL00474	52	-4	208	-9	NDNDN	NDN
AF99190	52	9	208	18	NDNDN	NDN
AF99243	52	20	208	-42	NDNDN	NDN
AS59833	52	-12	208	27	NDNDN	NDN
AS93648	52	-22	208	-7	NDNDN	NDN
AS59842	52	-4	208	41	NDNDN	NDN
AS76021	52	7	208	-2	NDNDN	NDN
AS93317	52	-14	208	9	NDNDN	NDN
AS93326	52	8	208	19	NDNDN	NDN
AS93344	52	-2	208	7	NDNDN	NDN
AS93639	52	3	208	10	NDNDN	NDN
AS76003	52	1	208	41	NDNDN	NDN

TABLE II. (Continued)

AT05045	52	2	208	0	NDNDN	NDN
AT11598	52	4	208	5	NDNDN	NDN
AT11623	52	- 9	208	11	NDNDN	NDN
AT11687	52	10	208	11	NDNDN	NDN
AT11696	52	11	208	4	NDNDN	NDN
AT11776	52	1	208	13	NDNDN	NDN
AT13814	13	16	52	23	NDNDN	NDN
AT11785	52	- 3	208	23	NDNDN	NDN
AV90320	52	23	208	15	NDNDN	NDN
AT13878	13	4	52	14	NDNDN	NDN
AT11794	52	5	208	29	NDNDN	NDN
AT13707	52	9	208	10	NDNDN	NDN
AT11856	52	15	208	28	NDNDN	NDN
AT13636	52	4	208	14	NDNDN	NDN
AT06882	52	8	208	22	NDNDN	NDN
AT11936	52	- 4	208	- 1	NDNDN	NDN
AT13716	52	- 1	208	27	NDNDN	NDN
AT17732	52	- 9	208	15	NDNDN	NDN
AT17769	52	- 10	208	- 2	NDNDN	NDN
AT89167	52	- 17	208	18	NDNDN	NDN
AT17876	52	- 24	208	- 1	NDNDN	NDN
AT89416	52	- 9	208	7	NDNDN	NDN
AT19227	52	- 7	208	- 1	NDNDN	NDN
AT70444	52	- 20	208	- 5	NDNDN	NDN
AT89158	52	- 15	208	- 11	NDNDN	NDN
AT17885	52	- 23	208	9	NDNDN	NDN
AT57825	52	- 21	208	- 15	NDNDN	NDN
AT89425	52	- 12	208	- 11	NDNDN	NDN
AT89461	52	- 37	208	- 13	NDNDN	NDN
AT95165	52	3	208	20	NDNDN	NDN
AT95218	52	- 11	208	3	NDNDN	NDN
AT95772	52	5	208	22	NDNDN	NDN
AU13300	52	3	208	17	NDNDN	NDN
AT95781	52	19	208	- 6	NDNDN	NDN
ZN07153	52	- 11	208	1	NDNDN	NDN
AT05063	52	- 11	208	3	NDNDN	NDN
AT96975	52	- 8	208	20	NDNDN	NDN
AT97043	52	12	208	26	NDNDN	NDN
AX27658	52	11	208	11	NDNDN	NDN
AU17031	52	- 5	208	8	NDNDN	NDN
AU50572	52	- 3	208	0	NDNDN	NDN
AU17059	13	- 2	52	14	NDNDN	NDN
AU67200	52	- 5	208	- 18	NDNDN	NDN
AU26405	52	- 6	208	8	NDNDN	NDN
AU67219	52	- 18	208	2	NDNDN	NDN
AU26432	52	- 9	208	12	NDNDN	NDN
AU26503	52	- 13	208	13	NDNDN	NDN
AU17095	52	- 39	208	10	NDNDN	NDN
AU26423	52	- 22	208	- 3	NDNDN	NDN
AU26478	52	- 4	208	5	NDNDN	NDN

TABLE II. (Continued)

AU67237	52	- 8	208	16	NDNDN NDN
AU67255	52	25	208	31	NDNDN NDN
AU73708	52	15	208	34	NDNDN NDN
AU73888	13	9	52	35	NDNDN NDN
AU73897	13	11	52	46	NDNDN NDN
AU73904	52	- 10	208	23	NDNDN NDN
AU92847	52	16	208	39	NDNDN NDN
AU92918	52	7	208	29	NDNDN NDN
AU93684	52	- 10	208	19	NDNDN NDN
AV00497	52	- 1	208	19	NDNDN NDN
AV00620	52	13	208	23	NDNDN NDN
AV05107	13	- 19	52	- 8	NDNDN NDN
AV05116	52	- 8	208	15	NDNDN NDN
AV12693	52	- 26	208	13	NDNDN NDN
AV12700	52	- 9	208	3	NDNDN NDN
AY91653	52	- 33	208	- 14	NDNDN NDN
ZE28385	52	- 4	208	18	NDNDN NDN
ZM89972	52	- 22	208	27	NDNDN NDN
ZN10034	13	4	52	- 1	NDNDN NDN
AU85815	52	- 13	208	20	NDNDN NDN
AV05965	52	- 24	208	- 10	NDNDN NDN
AV21772	52	22	208	12	NDNDN NDN
AV25510	52	0	208	9	NDNDN NDN
AV25501	52	15	208	11	NDNDN NDN
AV21898	52	2	208	4	NDNDN NDN
AV23945	52	- 1	208	29	NDNDN NDN
AV06695	52	5	208	11	NDNDN NDN
AV23963	52	13	208	19	NDNDN NDN
AV06702	52	0	208	21	NDNDN NDN
AV25529	52	- 12	208	30	NDNDN NDN
AV28280	52	4	208	10	NDNDN NDN
AV28299	52	2	208	- 2	NDNDN NDN
AV28315	52	15	208	- 5	NDNDN NDN
AV85427	52	- 18	208	25	NDNDN NDN
AV28333	52	- 19	208	23	NDNDN NDN
AV28351	13	- 2	52	- 5	NDNDN NDN
AV48068	52	- 1	208	11	NDNDN NDN
AV48951	52	- 4	208	10	NDNDN NDN
AV85409	52	- 12	208	34	NDNDN NDN
AV28342	52	- 12	208	- 6	NDNDN NDN
AV85436	52	2	208	8	NDNDN NDN
AV85463	52	3	208	25	NDNDN NDN
AV85472	52	- 9	208	17	NDNDN NDN
AV85481	52	20	208	25	NDNDN NDN
AV90384	52	- 12	208	19	NDNDN NDN
AV90535	52	8	208	20	NDNDN NDN
AV98924	52	- 2	208	22	NDNDN NDN
AV92271	52	- 18	208	4	NDNDN NDN
AV92280	52	- 4	208	12	NDNDN NDN
AV92306	52	- 9	208	15	NDNDN NDN

TABLE II. (Continued)

AV95487	52	-	9	208	-	3	NDNDN NDN
AV90795	52	-	7	208	-	2	NDNDN NDN
AW22676	52		33	208		14	NDNDN NDN
AX27701	52		23	208		8	NDNDN NDN
AW22890	52		25	208		27	NDNDN NDN
ZN31926	52		9	208		6	NDNDN NDN
AW42623	52		22	208		23	NDNDN NDN
AW02478	52		28	208		37	NDNDN NDN
AW22578	52	-	20	208		19	NDNDN NDN
BD28944	52	-	11	208		19	NDNDN NDN
AV79938	52		29	208		36	NDNDN NDN
AW22514	52		4	208		31	NDNDN NDN
AW43497	52		19	208		39	NDNDN NDN
AW49784	13		13	52		9	NDNDN NDN
AW91706	52	-	9	208		13	NDNDN NDN
AW96452	52		7	208		20	NDNDN NDN
AW96765	52		15	208		20	NDNDN NDN
AW96774	52		11	208		39	NDNDN NDN
AW96890	13		3	52		3	NDNDN NDN
AX20211	52		15	208		6	NDNDN NDN
AX21254	52		13	208		12	NDNDN NDN
AX26222	52		3	208		13	NDNDN NDN
AX26660	52		14	208		20	NDNDN NDN
AX28495	52		13	208		19	NDNDN NDN
AX46082	52	-	22	208	-	23	NDNDN NDN
AX58288	52	-	5	208	-	8	NDNDN NDN
AY59520	52	-	35	208	-	24	NDNDN NDN
ZM86211	52	-	38	208	-	29	NDNDN NDN
AD01430	52	-	6	208		12	NDNDN NDN
AX27050	52	-	36	208	-	34	NDNDN NDN
AX46073	52	-	19	208		12	NDNDN NDN
AX58000	52	-	7	208		0	NDNDN NDN
AX65550	52	-	11	208		6	NDNDN NDN
AX65569	52	-	3	208	-	6	NDNDN NDN
AX65578	52	-	20	208	-	19	NDNDN NDN
AX65587	52		9	208		3	NDNDN NDN
AX65621	52	-	5	208		0	NDNDN NDN
AX67198	52	-	6	208		20	NDNDN NDN
AX67205	13	-	3	52		1	NDNDN NDN
AX67214	52		2	208		3	NDNDN NDN
AX68480	52		15	208		15	NDNDN NDN
AX69512	52		4	208		0	NDNDN NDN
AX69521	52		11	208		2	NDNDN NDN
AX70122	52		14	208		15	NDNDN NDN
AX87243	52	-	26	208		0	NDNDN NDN
AX87752	52	-	3	208		1	NDNDN NDN
AY59511	52		3	208		17	NDNDN NDN
AY61244	52		4	208		22	NDNDN NDN
AY61486	52		6	208		18	NDNDN NDN
AY60265	52		24	208		15	NDNDN NDN

TABLE II. (Continued)

AY64147	52	- 4	208	22	NDNDN	NDN
ZM55976	52	7	208	25	NDNDN	NDN
AY59539	52	- 6	208	11	NDNDN	NDN
AY61226	52	6	208	30	NDNDN	NDN
AY61502	52	4	208	8	NDNDN	NDN
AY62358	52	- 2	208	7	NDNDN	NDN
ZM98257	52	9	208	13	NDNDN	NDN
ZP64868	13	- 5	52	0	NDNDN	NDN
AY64156	52	- 27	208	6	NDNDN	NDN
AY91411	52	- 18	208	- 11	NDNDN	NDN
AY64165	52	- 21	208	- 8	NDNDN	NDN
BB47190	52	- 39	208	- 2	NDNDN	NDN
AY64781	52	- 51	208	- 4	NDNDN	NDN
BE13171	52	0	208	- 11	NDNDN	NDN
ZP31449	52	- 24	208	- 17	NDNDN	NDN
AY64174	52	- 14	208	- 23	NDNDN	NDN
AY64807	52	- 26	208	- 27	NDNDN	NDN
BD38735	52	- 45	208	- 39	NDNDN	NDN
ZP21694	52	4	208	- 7	NDNDN	NDN
AY64790	52	17	208	- 3	NDNDN	NDN
AY91760	52	7	208	16	NDNDN	NDN
AY92703	52	23	208	12	NDNDN	NDN
AY95660	52	0	208	- 7	NDNDN	NDN
AY92954	52	1	208	3	NDNDN	NDN
AY95679	52	6	208	18	NDNDN	NDN
AY93700	52	- 9	208	16	NDNDN	NDN
AY95642	52	19	208	9	NDNDN	NDN
AY95651	52	30	208	25	NDNDN	NDN
AY93684	52	18	208	14	NDNDN	NDN
AY95553	52	15	208	4	NDNDN	NDN

TABLE III. **Summary of the activity of the reference compound, Glucantime (BL09186) against <u>Leishmania</u> <u>donovani</u> in the primary visceral test system during the period 1 January 1987 through 31 December 1989.**

BN	DOSE1	SUPPRES1	DOSE2	SUPPRES2	DOSE3	SUPPRES3	SD50
BL09186	208	91	416	94	NDNDN	NDN	113.
BL09186	104	51	208	69	416	95	101.
BL09186	52	28	104	66	208	80	81.8
BL09186	52	49	104	70	208	88	54.2
BL09186	26	47	52	39	208	68	110.
BL09186	26	2	52	55	208	64	50.1
BL09186	26	42	52	54	208	76	43.0
BL09186	26	8	52	29	208	84	110.
BL09186	26	23	52	32	208	71	123.
BL09186	26	28	52	55	208	90	46.7
BL09186	26	- 20	52	46	208	84	66.0
BL09186	26	27	52	34	208	77	109.
BL09186	26	21	52	57	208	88	47.9
BL09186	26	29	52	58	208	86	44.7
BL09186	26	16	52	53	208	84	53.6
BL09186	26	28	52	65	208	77	41.8
BL09186	26	24	52	51	208	79	53.1
BL09186	26	21	52	41	208	81	86.4
BL09186	26	24	52	81	208	93	35.4
BL09186	26	10	52	43	208	70	92.1
BL09186	26	18	52	47	208	81	65.3
BL09186	26	36	52	51	208	80	49.9
BL09186	26	37	52	48	208	86	59.6

TABLE III. (Continued)

BN	DOSE1	SUPPRES1	DOSE2	SUPPRES2	DOSE3	SUPPRES3	SD50
BL09186	26	25	52	65	208	85	41.9
BL09186	26	43	52	65	208	87	33.1
BL09186	26	10	52	54	208	96	49.4
BL09186	26	27	52	46	208	88	66.1
BL09186	26	33	52	64	208	90	38.9
BL09186	26	36	52	54	208	94	44.4
BL09186	26	30	52	59	208	89	43.6
BL09186	26	34	52	61	208	92	40.5
BL09186	26	46	52	69	208	98	30.1
BL09186	26	22	52	50	208	71	129.
BL09186	26	44	52	66	208	72	32.7
BL09186	26	24	52	44	208	93	68.4
BL09186	26	6	52	41	208	81	85.5
BL09186	26	49	52	67	208	89	27.3
BL09186	26	26	52	78	208	86	35.5
BL09186	26	26	52	54	208	85	48.3
BL09186	26	50	52	69	208	86	25.8
BL09186	26	10	52	26	208	74	128.
BL09186	26	33	52	43	208	76	84.1
BL09186	26	33	52	53	208	87	47.5
BL09186	26	21	52	43	208	81	79.8
BL09186	26	35	52	72	208	84	35.9
BL09186	26	18	52	30	208	72	125.
BL09186	26	16	52	39	208	81	91.8
BL09186	26	50	52	64	208	86	25.9
BL09186	26	19	52	56	208	85	49.8
BL09186	26	- 1	52	46	208	75	73.1
BL09186	26	15	52	50	208	85	115.
BL09186	26	29	52	49	208	67	60.4
BL09186	26	30	52	70	208	94	36.8
BL09186	26	8	52	40	208	77	92.9
BL09186	26	34	52	57	208	87	43.5
BL09186	26	46	52	64	208	85	31.4
BL09186	26	44	52	55	208	91	39.5
BL09186	26	30	52	47	208	82	64.1
BL09186	26	30	52	70	208	87	37.3
BL09186	26	28	52	57	208	86	45.9

TABLE III. (Continued)

Exp No.	Dose 1	Suppress 1	Dose 2	Suppress 2	Dose 3	Suppress 3
457	26	17	52	63	208	80
458	26	54	52	68	208	95
459	26	50	52	58	208	94
460	26	39	52	43	208	82
461	26	23	52	53	208	79
462	26	17	52	35	208	74
463	26	31	52	56	208	76
465	26	36	52	62	208	83
467	26	17	52	57	208	83
468	26	49	52	77	208	88
469	26	33	52	65	208	90
470	26	27	52	54	208	85
471	26	16	52	55	208	81
472	26	32	52	52	208	80
474	26	27	52	50	208	75
475	26	- 3	52	88	208	93
476	26	11	52	31	208	82
477	26	20	52	63	208	90
478	26	14	52	44	208	84
479	26	43	52	72	208	89
480	26	18	52	55	208	77
483	26	27	52	36	208	63
484	26	21	52	39	208	74
485	26	39	52	59	208	71
486	26	43	52	54	208	73
488	26	17	52	50	208	56
489	26	34	52	62	208	82
490	26	37	52	45	208	87
491	26	8	52	68	208	85
492	26	3	52	49	208	80

TABLE IV. Summary of the suppressive activity of WR06026 when administered orally to hamsters prior to infection with *Leishmania donovani*.

Treatment	Total mg/kg	Rx Schedule (day)	Mean No. Amastigotes	Percent Suppression
Vehicle Control	-	-1	655	-
WR06026	10	-3	67	90
	.1	-3	226	65
	.1	-2	398	39
	.1	-1	273	58
	.2	-3, -2	262	60
	.3	-3, -2, -1	323	51

TABLE V. Comparison of the antileishmanial activity of WR06026 when administered three days prior to infection (Group I) or three days postinfection (Group II and III).

Group	Rx Route	Dose mg/kg	Day of Necropsy*	Percent Suppression
I	PO**	1.6	+10	89
	PO	0.4	+10	55
	PO	0.1	+10	26
	PO	0.025	+10	10
II	PO	1.6	+ 7	100
	PO	0.4	+ 7	100
	PO	0.1	+ 7	86
	PO	0.025	+ 7	56
III	PO	1.6	+10	100
	PO	0.4	+10	100
	PO	0.1	+10	96
	PO	0.025	+10	37

* Posttreatment

** Per Os

TABLE VI. Suppressive activity in liver and spleen of WR06026 analogs administered either 3 days prior to or 3 days postinfection.

Compound	Dose*	% Supp. -3d#	(liver) +3d	% Supp. -3d#	(spleen) +3d
WR06026	1.6	71	100	44	65
	0.4	57	100	70	44
	0.1	14	85	46	56
BL52945	1.6	38	98	45	66
BL52196	1.6	0	91	59	53
BL52749	1.6	34	97	70	58
BL53308	1.6	19	96	46	36
BL34296	1.6	28	82	0	29

* Total mg/kg administered in single oral dose.

#-3d Drug given 3 days preinfection
+3d Drug given 3 days postinfection

TABLE VII. Effect of route of administration on efficacy of selected 8-aminoquinolines against *Leishmania donovani* in the golden hamster.

Compound	Dose(mg/kg)	% Suppression Route I.M.	P.O.
BK84200	0.20	0	2
	0.81	27	20
	3.25	98	95
ZP45845	0.20	- 6	26
	0.81	66	90
	3.25	99	90
BK99121	0.20	17	21
	0.81	80	76
	3.25	100	98
BL03308	0.20	25	18
	0.81	71	86
	3.25	98	100
BL50021	0.21	33	20
	0.81	70	73
	3.25	99	99
BL51297	0.21	37	13
	0.81	76	40
	3.25	98	99

TABLE VIII. Suppressive activity of combined sinefungin and purine analogs against *Leishmania donovani* in the golden hamster.*

Compound	Dose #	Alone	+Sinefungin +6.5#	+Sinefungin 3.25#
Sinefungin	-		59	48
Allopurinol riboside	104	-11	61	43
Oxyformycin B	104	18	73	34
Allopurinol	104	19	60	35
3-deazoguanosine	13	17	63	41
Thiopurinol riboside	13	18	41	44
Formycin B	3.25	22	57	51

*Results are expressed as % suppression of parasite numbers as compared to untreated controls.

#total mg/kg

TABLE IX. Effect of berberine analogs and Glucantime on numbers of amastigotes in livers of hamsters infected with *L. donovani*.

Compound	Dose(mg/kg)[a]	Suppression (%)[b]	% Wt. Change[b]
Berberine chloride (1)	52	20	+ 5
	208[c]	36	-10
Palmatine chloride (2)	52	14	0
	416	28	-11
Oxyberberine (3)	52	0	+ 9
	416	27	+ 6
Dihydroberberine (4)	52	23	+ 7
	416	34	+ 9
8-Cyano dihydroberberine (5)	52	22	+ 8
	208[c]	54	-18
Tetrahydroberberine N-oxide (6)	52	2	+ 8
	416	13	+11
Tetrahydroberberine (7)	52	17	+ 9
	416	50	+ 7
N-Methyl tetrahydro berberinium iodide (8)	52	10	+ 9
	416	56	-11
Berberine betaine (9)	52	15	+ 8
	416	23	-11
Glucantime[d]	52	72	+10
	208	84	+11

a. Total dose administered over a four day period.

b. As compared to animals receiving HEC-Tween vehicle only; each treatment group included 6 hamsters and 7 hamsters were included in the control groups.

c. Compounds administered at a maximum total dose of 208 mg/kg due to deaths among groups treated at 416 mg/kg in preliminary experiments.

d. Meglumine antimonate

TABLE X. Summary of the activity of the reference compound, Glucantime (BL09186) against <u>Leishmania</u> <u>braziliensis</u> <u>panamensis</u> in the primary cutaneous test system during the period 1 January through 31 December 1987.

BN	DOSE1	SUPPRES1	DOSE2	SUPPRES2	SD50
BL09186	208	73	832	83	140.
BL09186	52	21	208	66	150.
BL09186	208	55	832	77	188.

TABLE XI. Summary of active compounds in the primary cutaneous test system.

BN	DOSE1	SUPPRES1	DOSE2	SUPPRES2	DOSE3	SUPPRES3	SD50	SD50GLU	GI
AM16486	208	56	416	49	NDNDN	NDN	185.	162	.874
AM27167	208	50	416	71	NDNDN	NDN	207.	162	.78
AT63681	208	64	416	69	NDNDN	NDN	161.	167	1.03
BK84871	208	16	416	50	NDNDN	NDN	NDND	167	NDND
BLC5848	26	47	52	68	NDNDN	NDN	28.9	167	5.78
AS91313	208	49	416	63	NDNDN	NDN	222.	167	.752
BK71374	208	32	416	60	NDNDN	NDN	341.	192	.563
AR80315	208	26	416	51	NDNDN	NDN	407.	155	.379
AR80315	208	26	416	51	NDNDN	NDN	407.	155	.379
BL10956	13	23	104	79	208	78	56.3	717	12.7
BL10956	13	23	104	79	208	78	56.3	717	12.7
BK01845	13	0	26	36	52	53	45.4	717	15.7
BK01845	13	0	26	36	52	53	45.4	717	15.7
BL10956	26	59	104	79	208	66	21.8	660	30.2
BL10956	26	59	104	79	208	66	21.8	660	30.2
AJ15304	208	86	416	NDN	NDNDN	NDN	120.	312	2.58
ZP43609	208	20	416	60	NDNDN	NDN	363.	312	.857
AJ15304	208	86	416	NDN	NDNDN	NDN	120.	312	2.58
ZP43609	208	20	416	60	NDNDN	NDN	363.	312	.857
AT56097	52	22	208	56	NDNDN	NDN	180.	478	2.65

TABLE XII. Inactive compounds tested in the primary cutaneous test system.

BN	DOSE1	SUPPRES1	DOSE7	SUPPRES2	DOSE3	SUPPRES3
AL70010	208	9	4	-5	NDNDN	NDN
AL70225	208	4	416	13	NDNDN	NDN
AL70118	208	47	416	20	NDNDN	NDN
AL70145	208	21	416	25	NDNDN	NDN
AL70154	208	33	416	9	NDNDN	NDN
AL70163	208	-13	416	13	NDNDN	NDN
AL70092	208	8	416	21	NDNDN	NDN
BK84200	208	NDN	416	NDN	NDNDN	NDN
BK82457	208	-9	416	15	NDNDN	NDN
AL74401	208	-9	416	-1	NDNDN	NDN
AL74456	208	-17	416	3	NDNDN	NDN
AL74509	208	-1	416	-17	NDNDN	NDN
AL74518	208	-5	416	-9	NDNDN	NDN
AL74545	206	-9	416	7	NDNDN	NDN
AL74812	208	-1	416	-5	NDNDN	NDN
AL74723	208	-1	416	NDN	NDNDN	NDN
AL74714	208	-17	416	-17	NDNDN	NDN
AL81853	208	-21	416	-13	NDNDN	NDN
AL74750	208	11	416	26	NDNDN	NDN
AL81871	208	-21	416	17	NDNDN	NDN
AL74787	208	23	416	15	NDNDN	NDN
AL74634	208	-17	416	31	NDNDN	NDN
AL81764	208	-9	416	-17	NDNDN	NDN
AL81773	208	1	416	-21	NDNDN	NDN
AL74536	208	-1	416	-25	NDNDN	NDN
AL81880	208	6	416	-21	NDNDN	NDN
AL81942	208	4	416	-4	NDNDN	NDN
AL81997	208	7	416	11	NDNDN	NDN
AM00335	208	-7	416	-11	NDNDN	NDN
AM01430	208	4	416	0	NDNDN	NDN
AM00344	208	4	416	-11	NDNDN	NDN
AM01289	208	11	416	4	NDNDN	NDN
AM00497	208	30	416	0	NDNDN	NDN
AM01396	208	-4	416	7	NDNDN	NDN
AM01298	208	0	416	-7	NDNDN	NDN
AM01403	208	0	416	0	NDNDN	NDN
AM01305	208	4	416	4	NDNDN	NDN
AM00353	209	4	416	NDN	NDNDN	NDN
AM01369	208	19	416	0	NDNDN	NDN
AM01387	208	11	416	4	NDNDN	NDN
AM01350	208	4	416	4	NDNDN	NDN
AM01412	208	0	416	0	NDNDN	NDN
AM01421	208	19	416	2	NDNDN	NDN
AM00308	208	7	416	0	NDNDN	NDN
AM01476	208	5	416	14	NDNDN	NDN
AM01501	208	14	416	10	NDNDN	NDN
AM01716	208	14	416	11	NDNDN	NDN
AM01869	208	10	416	19	NDNDN	NDN

TABLE XII. (Continued)

AMO1565	208	19	416	14	NDNDN	NDN
1MO1887	208	9	416	32	NDNDN	NDN
AMO1645	208	0	416	14	NDNDN	NDN
AMO1912	46	0	208	5	NDNDN	NDN
AMO1485	208	14	416	0	NDNDN	NDN
AMO1752	208	7	416	NDN	NDNDN	NDN
AMO1725	208	26	416	- 10	NDNDN	NDN
AMO1707	208	10	416	- 19	NDNDN	NDN
AMO1529	208	- 24	416	0	NDNDN	NDN
AMO1958	208	30	416	5	NDNDN	NDN
AMO1967	208	11	416	5	NDNDN	NDN
AMO1985	208	3	416	NDN	NDNDN	NDN
AM16422	208	- 19	416	0	NDNDN	NDN
AM16459	208	23	416	- 14	NDNDN	NDN
AN64692	208	10	416	38	NDNDN	NDN
AM16539	208	14	416	21	NDNDN	NDN
AN83713	208	34	416	31	NDNDN	NDN
AM22297	208	21	416	28	NDNDN	NDN
AM27210	208	26	416	34	NDNDN	NDN
AM27014	208	21	416	26	NDNDN	NDN
·1083	208	10	416	24	NDNDN	NDN
AM27149	208	38	416	41	NDNDN	NDN
AM27176	208	38	416	38	NDNDN	NDN
AM27185	208	7	416	10	NDNDN	NDN
AM27087	208	3	416	45	NDNDN	NDN
AN04427	208	24	416	34	NDNDN	NDN
AN18403	208	14	416	14	NDNDN	NDN
AN62910	208	17	416	31	NDNDN	NDN
AM18588	208	24	416	32	NDNDN	NDN
AM27005	208	21	416	21	NDNDN	NDN
AP63878	208	10	416	- 10	NDNDN	NDN
AR15872	208	- 14	416	- 5	NDNDN	NDN
AP64026	208	0	416	19	NDNDN	NDN
AR16011	208	2	416	- 5	NDNDN	NDN
AQ03671	208	- 14	416	- 5	NDNDN	NDN
AQ46176	208	- 14	416	- 38	NDNDN	NDN
AQ46194	208	13	416	- 14	NDNDN	NDN
AP66182	208	5	416	- 19	NDNDN	NDN
AQ44065	208	5	416	- 19	NDNDN	NDN
AR16315	208	- 10	416	10	NDNDN	NDN
AR16520	208	- 19	416	- 29	NDNDN	NDN
AR18962	208	NDN	416	NDN	NDNDN	NDN
AS91313	208	16	416	- 10	NDNDN	NDN
AT63681	208	26	416	- 19	NDNDN	NDN
AU03377	208	14	416	- 10	NDNDN	NDN
AU29871	208	14	416	10	NDNDN	NDN
AU36376	208	- 17	416	8	NDNDN	NDN
AV00899	208	- 10	416	34	NDNDN	NDN
AV38866	208	- 12	416	4	NDNDN	NDN
AV78691	208	- 8	416	- 52	NDNDN	NDN

TABLE XII. (Continued)

AWO2423	208	-8	416	0	NDNDN	NDN
AW27475	208	-20	416	-2	NDNDN	NDN
BLO5419	208	NDN	416	NDN	NDNDN	NDN
AX87592	208	-4	416	0	NDNDN	NDN
ABO9374	208	0	416	0	NDNDN	NDN
BB47976	208	-33	416	-21	NDNDN	NDN
AB60760	416	0	NDNDN	NDN	NDNDN	NDN
ABO7665	208	-13	416	-13	NDNDN	NDN
AB61936	208	-38	416	-17	NDNDN	NDN
ABO8984	208	-33	416	-25	NDNDN	NDN
AX12406	208	4	416	-4	NDNDN	NDN
AY72283	208	-10	416	-13	NDNDN	NDN
BG45726	208	-13	416	-35	NDNDN	NDN
AB84331	208	-13	416	-4	NDNDN	NDN
AB91498	208	0	416	0	NDNDN	NDN
AC42614	208	-13	416	-8	NDNDN	NDN
AC46041	208	10	416	10	NDNDN	NDN
AC47404	208	3	416	14	NDNDN	NDN
AC79960	208	-3	416	42	NDNDN	NDN
AD30799	208	7	416	14	NDNDN	NDN
AC80098	208	10	416	10	NDNDN	NDN
AD34760	208	17	416	14	NDNDN	NDN
AD27827	208	7	416	10	NDNDN	NDN
AD37350	208	10	416	0	NDNDN	NDN
AD30011	208	24	416	34	NDNDN	NDN
AC79924	208	3	416	-8	NDNDN	NDN
AC80089	208	3	416	13	NDNDN	NDN
ADO7263	208	0	416	-3	NDNDN	NDN
AD37672	208	-10	416	14	NDNDN	NDN
AD38151	208	14	416	10	NDNDN	NDN
AD87047	208	7	416	0	NDNDN	NDN
AE15019	208	-20	416	28	NDNDN	NDN
AE32921	208	3	416	14	NDNDN	NDN
AE37480	208	-19	416	30	NDNDN	NDN
AJ63686	208	7	416	42	NDNDN	NDN
AF24602	208	0	416	10	NDNDN	NDN
AJ64905	208	5	416	37	NDNDN	NDN
AJ48107	208	-10	416	-14	NDNDN	NDN
AJ64932	208	-19	416	5	NDNDN	NDN
AJ52165	208	-5	416	10	NDNDN	NDN
AE36018	208	5	416	5	NDNDN	NDN
AE57464	208	5	416	-14	NDNDN	NDN
AJ30098	208	-5	416	10	NDNDN	NDN
AJ66329	208	-5	416	5	NDNDN	NDN
AJ64950	208	16	416	14	NDNDN	NDN
AJ77957	208	-10	416	0	NDNDN	NDN
AJ65135	208	10	416	0	NDNDN	NDN
AJ65171	208	0	416	5	NDNDN	NDN
AJ66221	208	0	416	5	NDNDN	NDN
AJ66285	208	-10	416	-10	NDNDN	NDN

TABLE XII. (Continued)

AJ64978	208	- 29	416	- 24	NDNDN	NDN
AJ65153	208	5	416	19	NDNDN	NDN
AJ82163	208	- 8	416	- 5	NDNDN	NDN
AJ82190	208	- 26	416	- 11	NDNDN	NDN
AJ82207	208	- 11	416	- 16	NDNDN	NDN
AJ82261	208	- 5	416	5	NDNDN	NDN
AJ82270	208	- 11	416	7	NDNDN	NDN
AJ82369	208	- 3	416	- 11	NDNDN	NDN
AJ84676	208	- 11	416	- 21	NDNDN	NDN
AK85678	208	0	416	- 4	NDNDN	NDN
BL07682	208	42	416	NDN	NDNDN	NDN
AK86148	208	8	416	0	NDNDN	NDN
AK34582	208	0	416	- 4	NDNDN	NDN
AK86193	208	8	416	8	NDNDN	NDN
AK54333	208	- 4	416	12	NDNDN	NDN
AK53649	208	8	416	0	NDNDN	NDN
AK72859	208	- 8	416	0	NDNDN	NDN
AK85196	208	8	416	0	NDNDN	NDN
AK85338	208	- 8	416	4	NDNDN	NDN
AK85150	208	- 4	416	8	NDNDN	NDN
AK74719	208	- 8	416	31	NDNDN	NDN
AK84028	208	8	416	8	NDNDN	NDN
AK83950	208	- 4	416	- 8	NDNDN	NDN
AK85650	208	- 8	416	0	NDNDN	NDN
AK34546	208	4	416	- 4	NDNDN	NDN
AK52928	208	4	416	8	NDNDN	NDN
AK85178	208	- 4	416	- 8	NDNDN	NDN
AK28244	208	- 8	416	4	NDNDN	NDN
BK56537	208	NDN	416	NDN	NDNDN	NDN
ZP11278	208	8	416	42	NDNDN	NDN
AK31714	208	12	416	0	NDNDN	NDN
AK86504	208	0	416	8	NDNDN	NDN
AY71553	208	- 8	416	- 8	NDNDN	NDN
AK30066	208	- 12	416	15	NDNDN	NDN
AK86406	208	- 12	416	0	NDNDN	NDN
BK75916	208	8	416	4	NDNDN	NDN
BK75738	104	8	208	0	NDNDN	NDN
BK73850	208	NDN	416	NDN	NDNDN	NDN
AL42669	208	- 13	416	8	NDNDN	NDN
BK78060	208	0	416	- 25	NDNDN	NDN
BK77947	208	0	416	0	NDNDN	NDN
AL40192	208	4	416	0	NDNDN	NDN
AL19615	208	4	416	4	NDNDN	NDN
BK81843	208	- 8	416	21	NDNDN	NDN
AL07697	208	4	416	14	NDNDN	NDN
BK83365	208	- 17	416	- 20	NDNDN	NDN
AL02174	208	- 17	416	- 13	NDNDN	NDN
BK78079	208	- 13	416	5	NDNDN	NDN
AL19599	208	- 17	416	- 8	NDNDN	NDN
BK83374	208	- 4	416	4	NDNDN	NDN

TABLE XII. (Continued)

BK83418	208	8	416	-4	NDNDN	NDN
BK81843	208	-8	416	21	NDNDN	NDN
BK82804	208	0	416	-13	NDNDN	NDN
AL38012	208	4	416	-4	NDNDN	NDN
BL04387	208	25	416	-6	NDNDN	NDN
BK85387	208	3	416	37	NDNDN	NDN
ZP23714	26	28	52	25	NDNDN	NDN
ZP43261	26	19	52	25	NDNDN	NDN
BL04663	208	6	416	28	NDNDN	NDN
BK84979	208	25	416	39	NDNDN	NDN
BK84862	208	3	416	17	NDNDN	NDN
BK84844	208	-3	416	12	NDNDN	NDN
BK85083	208	3	416	28	NDNDN	NDN
BL04930	208	41	416	44	NDNDN	NDN
ZP46833	26	25	52	19	NDNDN	NDN
BL04976	208	12	416	14	NDNDN	NDN
AS34514	208	-8	416	0	NDNDN	NDN
AS39500	208	4	416	15	NDNDN	NDN
BL05419	208	8	416	8	NDNDN	NDN
AF35990	208	4	416	27	NDNDN	NDN
AS26629	208	4	416	19	NDNDN	NDN
AS25720	208	-4	416	4	NDNDN	NDN
AS35726	208	19	416	23	NDNDN	NDN
AS25793	208	4	416	12	NDNDN	NDN
AS26861	208	23	416	23	NDNDN	NDN
AS25837	208	-15	416	23	NDNDN	NDN
AS40478	208	12	416	12	NDNDN	NDN
AF47543	208	-8	416	-15	NDNDN	NDN
AS25748	208	-12	416	15	NDNDN	NDN
AS40441	208	4	416	8	NDNDN	NDN
AS37006	208	-8	416	8	NDNDN	NDN
AS35762	208	12	416	12	NDNDN	NDN
AF96742	208	-30	416	-3	NDNDN	NDN
AF48317	208	30	416	27	NDNDN	NDN
BL09533	208	40	416	NDN	NDNDN	NDN
BK85869	208	-7	416	3	NDNDN	NDN
AF97267	208	10	416	-24	NDNDN	NDN
AF97169	208	12	416	-3	NDNDN	NDN
BK85878	208	3	416	5	NDNDN	NDN
AS33937	208	-10	416	-12	NDNDN	NDN
BK98839	208	10	416	-7	NDNDN	NDN
BK96826	208	-13	416	-10	NDNDN	NDN
AF97123	208	0	416	10	NDNDN	NDN
AF97178	208	3	416	-27	NDNDN	NDN
BL05802	208	-7	416	3	NDNDN	NDN
BL09373	208	NDN	416	NDN	NDNDN	NDN
BL09524	208	10	416	-15	NDNDN	NDN
AF97043	208	0	416	7	NDNDN	NDN
AG88905	208	11	416	14	NDNDN	NDN
AG50769	208	-4	416	29	NDNDN	NDN

TABLE XII. (Continued)

AG75766	208	0	416	10	NDNDN	NDN
AG45679	208	7	416	14	NDNDN	NDN
AG42114	208	4	416	18	NDNDN	NDN
AG75766	208	0	416	10	NDNDN	NDN
AG45679	208	7	416	14	NDNDN	NDN
AD90722	208	11	416	7	NDNDN	NDN
AG51346	208	- 7	416	14	NDNDN	NDN
AG47002	208	- 11	416	- 4	NDNDN	NDN
AG39920	208	4	416	0	NDNDN	NDN
AG88905	208	11	416	14	NDNDN	NDN
AG47002	208	- 11	416	- 4	NDNDN	NDN
AG51346	208	- 7	416	14	NDNDN	NDN
AK16379	208	- 24	416	25	NDNDN	NDN
BL05580	208	43	416	NDN	NDNDN	NDN
AT53434	208	32	416	34	NDNDN	NDN
AG44494	208	4	416	32	NDNDN	NDN
AG39911	208	7	416	- 14	NDNDN	NDN
AG39920	208	4	416	0	NDNDN	NDN
BL05599	208	- 14	416	14	NDNDN	NDN
AG39911	208	7	416	- 14	NDNDN	NDN
AG44494	208	4	416	32	NDNDN	NDN
AG39564	208	- 7	416	4	NDNDN	NDN
AH62335	208	26	416	18	NDNDN	NDN
BL05599	208	- 14	416	14	NDNDN	NDN
AG50769	208	- 4	416	29	NDNDN	NDN
AH62335	208	26	416	18	NDNDN	NDN
AT53434	208	32	416	34	NDNDN	NDN
BL05580	208	43	416	NDN	NDNDN	NDN
AK16379	208	- 24	416	25	NDNDN	NDN
AD90722	208	11	416	7	NDNDN	NDN
AG39564	208	- 7	416	4	NDNDN	NDN
AG42114	208	4	416	18	NDNDN	NDN
AR79090	208	- 16	416	- 16	NDNDN	NDN
AR78780	208	- 16	416	- 15	NDNDN	NDN
BL10796	208	- 24	416	- 24	NDNDN	NDN
AM73623	208	4	416	- 8	NDNDN	NDN
AR79090	208	- 16	416	- 16	NDNDN	NDN
AF63225	208	0	416	- 10	NDNDN	NDN
AR79152	208	- 16	416	- 14	NDNDN	NDN
AK63190	208	- 8	416	12	NDNDN	NDN
AR79107	208	- 8	416	- 12	NDNDN	NDN
AR45432	208	4	416	NDN	NDNDN	NDN
AF01814	208	- 4	416	32	NDNDN	NDN
BL05606	208	- 24	416	- 25	NDNDN	NDN
AK63190	208	- 8	416	12	NDNDN	NDN
AR45432	208	4	416	NDN	NDNDN	NDN
BL10607	208	4	416	20	NDNDN	NDN
AR79107	208	- 8	416	- 12	NDNDN	NDN
BL10796	208	- 24	416	- 24	NDNDN	NDN
AR78780	208	- 16	416	- 15	NDNDN	NDN

TABLE XII. (Continued)

AR63225	208	0	416	-10	NDNDN	NDN
AR79152	208	-16	416	-14	NDNDN	NDN
BL10607	208	4	416	20	NDNDN	NDN
AR79134	208	-16	416	-12	NDNDN	NDN
AR01814	208	-4	416	32	NDNDN	NDN
BL05606	208	-24	416	-25	NDNDN	NDN
BL10590	208	-15	416	-16	NDNDN	NDN
BL10714	208	4	416	4	NDNDN	NDN
AR79134	208	-16	416	-12	NDNDN	NDN
BL10714	208	4	416	4	NDNDN	NDN
AM73623	208	4	416	-8	NDNDN	NDN
BL10590	208	-15	416	-16	NDNDN	NDN
AR79885	208	NDN	416	NDN	NDNDN	NDN
AR79965	208	19	416	NDN	NDNDN	NDN
AR79787	208	40	416	27	NDNDN	NDN
AR80379	208	-7	416	-16	NDNDN	NDN
AR79965	208	19	416	NDN	NDNDN	NDN
AR80351	208	28	416	-23	NDNDN	NDN
AR79223	208	40	416	NDN	NDNDN	NDN
AR80379	208	-7	416	-16	NDNDN	NDN
AR80244	208	19	416	NDN	NDNDN	NDN
AR80244	208	19	416	NDN	NDNDN	NDN
AR80333	208	-7	416	30	NDNDN	NDN
AR80342	208	-4	416	47	NDNDN	NDN
AR79223	208	40	416	NDN	NDNDN	NDN
AR80299	208	10	416	4	NDNDN	NDN
AR80360	208	-10	416	25	NDNDN	NDN
AR80342	208	-4	416	47	NDNDN	NDN
AR79885	208	NDN	416	NDN	NDNDN	NDN
AR80351	208	28	416	-23	NDNDN	NDN
AR80360	208	-10	416	25	NDNDN	NDN
AR79787	208	40	416	27	NDNDN	NDN
AR80333	208	-7	416	30	NDNDN	NDN
AR80299	208	10	416	4	NDNDN	NDN
AR84984	208	0	416	8	NDNDN	NDN
AR91863	208	3	416	NDN	NDNDN	NDN
AR91890	208	-12	416	4	NDNDN	NDN
BH32724	6.5	19	26	25	52	27
AR94337	208	4	416	4	NDNDN	NDN
AR94355	208	-4	416	-8	NDNDN	NDN
BL12521	104	33	416	12	3328	47
BK46362	104	21	208	NDN	832	NDN
AR91863	208	3	416	NDN	NDNDN	NDN
AR84304	208	38	416	44	NDNDN	NDN
AR94355	208	-4	416	-8	NDNDN	NDN
AR94364	208	23	416	27	NDNDN	NDN
AR94364	208	23	416	27	NDNDN	NDN
AR94417	208	4	416	0	NDNDN	NDN
AR91854	208	9	416	-27	NDNDN	NDN
AR91890	208	-12	416	4	NDNDN	NDN

TABLE XII. (Continued)

AR84304	208	38	416	44	NDNDN	NDN
BH32724	6.5	19	26	25	52	27
AR84984	208	0	416	8	NDNDN	NDN
AS76405	208	- 8	416	15	NDNDN	NDN
AR94337	208	4	416	4	NDNDN	NDN
BL12521	104	33	416	12	3328	47
AR91854	208	9	416	- 27	NDNDN	NDN
AS76405	208	- 8	416	15	NDNDN	NDN
AR94373	208	12	416	8	NDNDN	NDN
AR94417	208	4	416	0	NDNDN	NDN
BK46362	104	21	208	NDN	832	NDN
AR94373	208	12	416	8	NDNDN	NDN
BL12227	208	7	416	7	NDNDN	NDN
BL12263	208	10	416	- 3	NDNDN	NDN
BL10956	26	7	104	24	208	44
BL12245	208	0	416	3	NDNDN	NDN
BL12236	208	- 3	416	0	NDNDN	NDN
BL12503	208	NDN	416	NDN	NDNDN	NDN
BL12254	208	7	416	10	NDNDN	NDN
BL11373	208	7	416	- 3	NDNDN	NDN
BL12254	208	7	416	10	NDNDN	NDN
BL11364	208	10	416	10	NDNDN	NDN
BL12263	208	10	416	- 3	NDNDN	NDN
BL11391	208	3	416	10	NDNDN	NDN
BL12503	208	NDN	416	NDN	NDNDN	NDN
AT20211	208	14	416	0	NDNDN	NDN
BL11391	208	3	416	10	NDNDN	NDN
BL12236	208	- 3	416	0	NDNDN	NDN
BL12245	208	0	416	3	NDNDN	NDN
BL11373	208	7	416	- 3	NDNDN	NDN
BL12227	208	7	416	7	NDNDN	NDN
BL10956	26	7	104	24	208	44
BL11364	208	10	416	10	NDNDN	NDN
AT20211	208	14	416	0	NDNDN	NDN
BL11382	208	- 3	416	- 3	NDNDN	NDN
BL11382	208	- 3	416	- 3	NDNDN	NDN
BL12361	208	3	416	23	NDNDN	NDN
BK40440	208	- 3	416	13	NDNDN	NDN
BL12290	208	- 7	416	3	NDNDN	NDN
BK40557	208	3	416	30	NDNDN	NDN
BL12281	208	- 3	416	17	NDNDN	NDN
BL12343	208	- 7	416	13	NDNDN	NDN
BL12352	208	27	416	23	NDNDN	NDN
BL12334	208	0	416	3	NDNDN	NDN
BL12272	208	- 3	416	27	NDNDN	NDN
BL12325	208	23	416	20	NDNDN	NDN
BL12307	208	- 7	416	12	NDNDN	NDN
BL12316	208	- 4	416	23	NDNDN	NDN
BK40459	208	3	416	23	NDNDN	NDN
BK40548	208	- 23	416	- 10	NDNDN	NDN

TABLE XII. (Continued)

BL12272	208	-3	416	27	NDNDN	NDN
BK40413	208	0	416	18	NDNDN	NDN
BK40422	208	-3	416	30	NDNDN	NDN
BK40431	208	17	416	23	NDNDN	NDN
BL12343	208	-7	416	13	NDNDN	NDN
BL12352	208	27	416	23	NDNDN	NDN
BK40413	208	0	416	18	NDNDN	NDN
BL12361	208	3	416	23	NDNDN	NDN
BK40431	208	17	416	23	NDNDN	NDN
BK40440	208	-3	416	13	NDNDN	NDN
BK40557	208	3	416	30	NDNDN	NDN
BL12325	208	23	416	20	NDNDN	NDN
BL12334	208	0	416	3	NDNDN	NDN
BK40459	208	3	416	23	NDNDN	NDN
BK40548	208	-23	416	-10	NDNDN	NDN
BK40422	208	-3	416	30	NDNDN	NDN
BL12281	208	-3	416	17	NDNDN	NDN
BL12290	208	-7	416	3	NDNDN	NDN
BL12307	208	-7	416	12	NDNDN	NDN
BL12316	208	-4	416	23	NDNDN	NDN
BL12370	208	6	416	41	NDNDN	NDN
BK40351	208	-20	416	-9	NDNDN	NDN
BL12389	208	-19	416	1	NDNDN	NDN
BK40324	208	-5	416	17	NDNDN	NDN
BK40342	208	-35	416	-4	NDNDN	NDN
BK40333	208	34	416	NDN	NDNDN	NDN
BH58880	208	-9	416	21	NDNDN	NDN
BL12398	208	5	416	13	NDNDN	NDN
BK71678	208	-39	416	-4	NDNDN	NDN
AL18707	208	-14	416	1	NDNDN	NDN
BB26342	208	-19	416	1	NDNDN	NDN
AV15523	208	-49	416	-24	NDNDN	NDN
AL18707	208	-14	416	1	NDNDN	NDN
AC43817	208	-22	416	-29	NDNDN	NDN
BJ22269	208	-14	416	27	NDNDN	NDN
BB26342	208	-19	416	1	NDNDN	NDN
AB12693	208	-24	416	-17	NDNDN	NDN
BK40324	208	-5	416	17	NDNDN	NDN
BL12370	208	6	416	41	NDNDN	NDN
AC43817	208	-22	416	-29	NDNDN	NDN
AV15523	208	-49	416	-24	NDNDN	NDN
BL12389	208	-19	416	1	NDNDN	NDN
BH58880	208	-9	416	21	NDNDN	NDN
BL12405	208	-49	416	-39	NDNDN	NDN
BK40333	208	34	416	NDN	NDNDN	NDN
BJ22269	208	-14	416	27	NDNDN	NDN
BL12398	208	5	416	13	NDNDN	NDN
AB12693	208	-24	416	-17	NDNDN	NDN
BL12405	208	-49	416	-39	NDNDN	NDN
BK40342	208	-35	416	-4	NDNDN	NDN

TABLE XII. (Continued)

BK71678	208 - 39	416 - 4	NDNDN	NDN
BK40351	208 - 20	416 - 9	NDNDN	NDN
AG75480	208 33	416 49	NDNDN	NDN
ZM65703	208 - 39	416 2	NDNDN	NDN
BE19075	208 - 52	416 - 8	NDNDN	NDN
BL13886	208 - 45	416 - 27	NDNDN	NDN
BC08705	208 - 14	416 9	NDNDN	NDN
BD54202	208 - 20	416 17	NDNDN	NDN
AH88857	208 NDN	416 NDN	NDNDN	NDN
BB50213	208 NDN	416 NDN	NDNDN	NDN
BC09766	208 - 33	416 47	NDNDN	NDN
ZM67841	208 - 12	416 29	NDNDN	NDN
ZN07519	208 - 22	416 - 8	NDNDN	NDN
BE17580	208 NDN	416 NDN	NDNDN	NDN
ZN07519	208 - 22	416 - 8	NDNDN	NDN
BC09766	208 - 33	416 47	NDNDN	NDN
BE17580	208 NDN	416 NDN	NDNDN	NDN
BD54202	208 - 20	416 17	NDNDN	NDN
BC08705	208 - 14	416 9	NDNDN	NDN
AH88857	208 NDN	416 NDN	NDNDN	NDN
BB50213	208 NDN	416 NDN	NDNDN	NDN
AG91144	208 NDN	416 NDN	NDNDN	NDN
BE19075	208 - 52	416 - 8	NDNDN	NDN
BL13886	208 - 45	416 - 27	NDNDN	NDN
ZM65703	208 - 39	416 2	NDNDN	NDN
ZM67841	208 - 12	416 29	NDNDN	NDN
AG91144	208 NDN	416 NDN	NDNDN	NDN
AG75480	208 33	416 49	NDNDN	NDN
AW01042	208 NDN	416 NDN	NDNDN	NDN
AJ56761	208 - 13	416 44	NDNDN	NDN
AW01042	208 NDN	416 NDN	NDNDN	NDN
AU67915	208 - 17	416 4	NDNDN	NDN
BL22241	208 - 43	416 - 22	NDNDN	NDN
BL22241	208 - 43	416 - 22	NDNDN	NDN
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BE15451	208 30	416 NDN	NDNDN	NDN
AU67915	208 - 17	416 4	NDNDN	NDN
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BL21155	208 - 17	416 - 17	NDNDN	NDN
BL21155	208 - 17	416 - 17	NDNDN	NDN
BL45226	52 - 11	208 7	NDNDN	NDN
BL45191	52 11	208 5	NDNDN	NDN
BL45217	52 - 6	208 25	NDNDN	NDN
BL45217	52 - 6	208 25	NDNDN	NDN
BL45235	44 7	180 11	NDNDN	NDN
BL45262	52 - 7	208 - 14	NDNDN	NDN
BL45244	52 - 4	208 4	NDNDN	NDN
BL45235	44 7	180 11	NDNDN	NDN
BL45244	52 - 4	208 4	NDNDN	NDN
BL45262	52 - 7	208 - 14	NDNDN	NDN

TABLE XII. (Continued)

BL45182	52	39	208	46	NDNDN	NDN
BL45182	52	39	208	46	NDNDN	NDN
BL45208	52	44	208	49	NDNDN	NDN
BL45253	52	-11	208	21	NDNDN	NDN
BL45253	52	-11	208	21	NDNDN	NDN
BL45226	52	-11	208	7	NDNDN	NDN
BL45191	52	11	208	5	NDNDN	NDN
BL45208	52	44	208	49	NDNDN	NDN
BL01653	208	10	416	16	NDNDN	NDN
BL01662	208	-3	416	6	NDNDN	NDN
BL01608	208	13	416	23	NDNDN	NDN
BL01671	208	23	416	32	NDNDN	NDN
BL01626	208	16	416	23	NDNDN	NDN
BL01617	208	13	416	23	NDNDN	NDN
BL01680	208	-10	416	16	NDNDN	NDN
BL01617	208	13	416	23	NDNDN	NDN
BL01635	208	6	416	29	NDNDN	NDN
BL01644	208	13	416	26	NDNDN	NDN
BL47024	52	-39	208	-13	NDNDN	NDN
BL05802	208	10	416	13	NDNDN	NDN
BL01608	208	13	416	23	NDNDN	NDN
BL01662	208	-3	416	6	NDNDN	NDN
BL01626	208	16	416	23	NDNDN	NDN
BL01671	208	23	416	32	NDNDN	NDN
BL05802	208	10	416	13	NDNDN	NDN
BL01635	208	6	416	29	NDNDN	NDN
AE80043	208	-10	416	-6	NDNDN	NDN
BL47042	52	-13	208	0	NDNDN	NDN
BL01644	208	13	416	26	NDNDN	NDN
BL01680	208	-10	416	16	NDNDN	NDN
BL01653	208	10	416	16	NDNDN	NDN
AE80043	208	-10	416	-6	NDNDN	NDN
BL47024	52	-39	208	-13	NDNDN	NDN
BL47042	52	-13	208	0	NDNDN	NDN

TABLE XIII. Effect of berberine analogs and Glucantime on lesion size of hamsters infected with *L. braziliensis panamensis*.

Compound	Dose (mg/kg)[a]	Suppression (%)[b]	% Wt. Change[b]
Berberine chloride (1)	52	22	- 2
	208	56	- 1
Palmatine chloride (2)	52	0	0
	208	0	- 6
Oxyberberine (3)	52	0	+15
	208	21	0
Dihydroberberine (4)	52	0	+ 1
	208	3	- 1
8-Cyano dihydroberberine (5)	52	39	- 1
	208	46	- 6
Tetrahydroberberine N-oxide (6)	52	8	+ 1
	208	11	- 1
Tetrahydro berberine (7)	52	0	0
	208	26	- 1
N-Methyl tetrahydro berberinium iodine (8)	52	0	0
	208	8	- 5
Berberine betaine (9)	52	11	+ 2
	208	5	- 5
Glucantime[c]	52	22	+ 2
	208	66	- 3

a. Total dose administered over a four day period.

b. As compared to animals receiving HEC-Tween vehicle only; each treatment group consisted of 6 hamsters, and 7 hamsters were included in the control group.

c. Meglumine antimonate

TABLE XIV. Summary of the suppressive activity of compounds studied in the primary visceral test system during the technical extension of this contract.

BN	DOSE1	SUPPRES1	DOSE2	SUPPRES2	DOSE3	SUPPRES3
AY96961	52	17	208	2	NDNDN	NDN
BK70117	52	0	208	- 8	NDNDN	NDN
AY96354	52	- 5	208	1	NDNDN	NDN
AY95688	52	- 21	208	0	NDNDN	NDN
AY96345	52	8	208	- 5	NDNDN	NDN
AY96201	52	24	208	28	NDNDN	NDN
AY96372	52	9	208	- 4	NDNDN	NDN
AY96336	52	15	208	- 16	NDNDN	NDN
AY96318	52	- 4	208	22	NDNDN	NDN
AY95697	52	- 26	208	12	NDNDN	NDN
AY96327	52	4	208	- 26	NDNDN	NDN
AR32604	52	- 1	208	24	416	44
AR45469	52	6	208	12	416	10
AT00022	52	- 12	208	5	416	37
AU50581	52	4	208	28	416	9
BL07048	52	24	208	22	416	3
BL07628	52	10	208	19	416	NDN

TABLE XV. Suppressive activity of oxyformycin B (BK74731) and sinefungin (BL58705) when administered alone or in combination to *L. donovani* infected hamsters

Compound	Total Dosage*	Percent Weight Change	Percent Suppression
Vehicle	-	+7	-
Glucantime (BL09186)	208	+8	83
	52	+7	43
	26	+5	34
Sinefungin Alone BL58705	13	+7	81
	6.5	+9	71
	3.25	+7	52
Oxyformycin B Alone BK74731	208	+8	21
BL58705 + BK74731	13 208	+6	84
BL58705 + BK74731	6.5 208	+8	72
BL58705 + BK74731	3.25 208	+3	58

*mg/kg

AD-A253 305 TESTING OF EXPERIMENTAL COMPOUNDS FOR EFFICACY AGAINST LEISHMANIA(U) GEORGIA UNIV RESEARCH FOUNDATION INC ATHENS W L HANSON ET AL. 31 OCT 90 XA-USAMRDC 2/2

UNCLASSIFIED DAMD17-85-C-5012 F/G 6/5 NL

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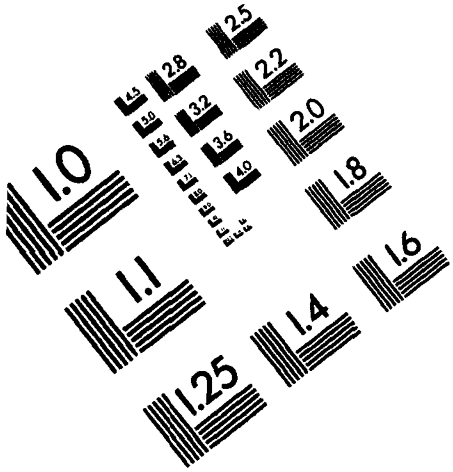

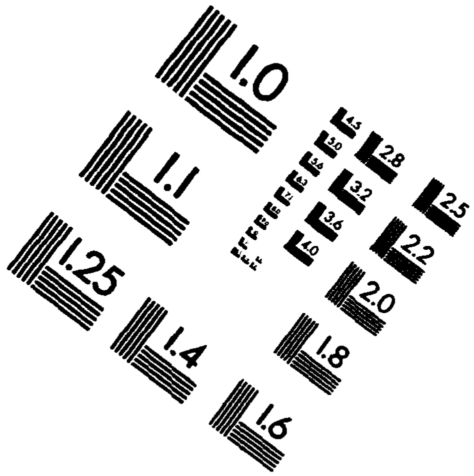

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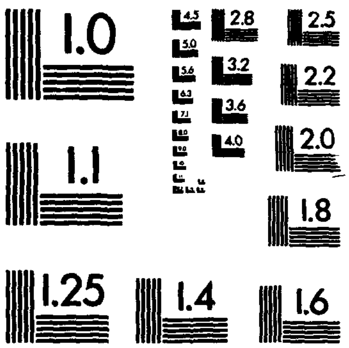

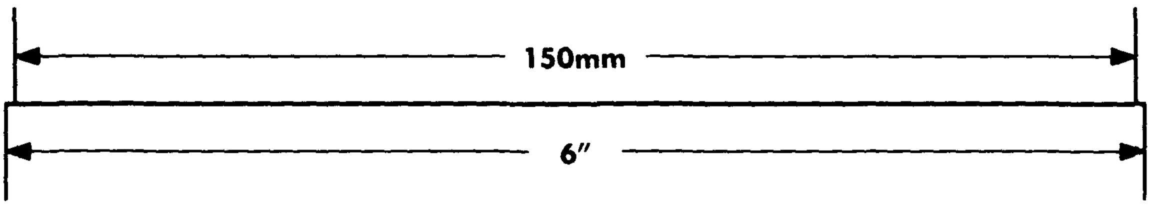

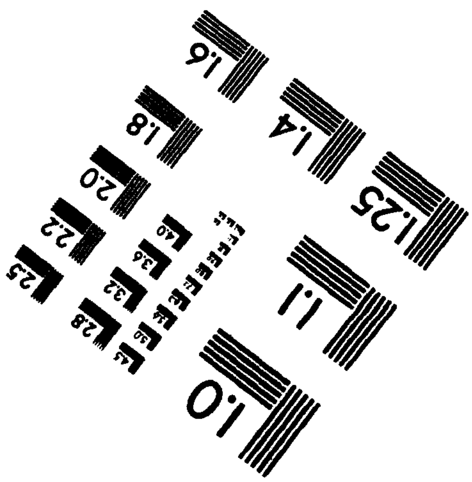

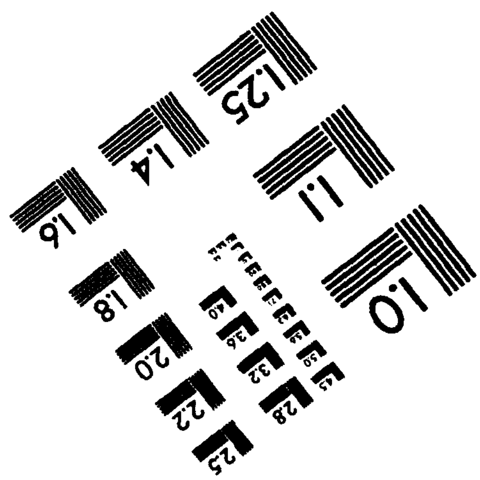

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TABLE XVI. Suppressive activity of combinations of paromomycin (BL53531) and gentamycin sulfate or paromomycin and neomycin (AJ57795) when administered via the intraperitoneal route against *Leishmania donovani* in the hamster.

Compound	Total Dosage*	Percent Weight Change	Percent Suppression
Vehicle	-	+7	-
Glucantime BL09186	208	+7	44
	52	+8	25
	26	+7	21
Paromomycin Alone BL53531	900	+9	30
	700	+6	11
	500	+6	17
Gentamycin Sulfate Alone**	1200	+4	36
Neomycin Alone AJ57795	700	+8	20
BL53531 + Gentamycin Sulfate	900 1200	-2	40
BL53531 + Gentamycin Sulfate	700 1200	+2	37
BL53551 + Gentamycin Sulfate	500 1200	-2	34
BL53531 + AJ57795	900 700	+4	28
BL53531 + AJ57795	700 700	+4	34
BL53531 + AJ57795	500 700	+5	27

* mg/kg
** yields total dose of 700 mg/kg Gentamycin

TABLE XVII. The suppressive activity of liposomal muramyl tripeptide (MTP) alone or in combination with Glucantime (BL09186) against *Leishmania donovani*.

Compound	Total Dosage	Percent Weight Change	Percent Suppression
Vehicle	-	+ 7	-
BL09186	208 mg/kg	+ 7	44
	52 mg/kg	+ 7	30
MTP Alone	400 μg	-11	-35
MTP + BL09186	400 μg 208 mg/kg	- 6	79
MTP + BL09186	400 μg 52 mg/kg	-10	25
MTP Alone	200 μg	+ 3	-35
MTP + BL09186	200 μg 208 mg/kg	- 1	49
MTP + BL09186	200 μg 52 mg/kg	+ 1	-18

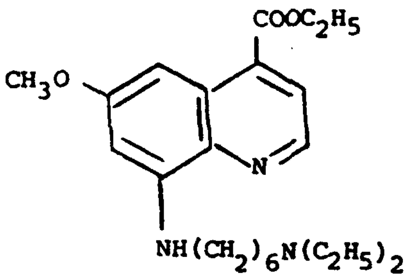
TABLE XVIII. Summary of results obtained from the optimization studies of sinefungin (BL58705) in hamsters infected with *Leishmania donovani*

Treatment	Total Dosage*	Regimen	Percent Weigth Change	Percent Suppression
Vehicle	-	qd x 1 day	+12	-
		qd x 2 days	+ 3	-
		qd x 4 days	+ 7	-
		bid x 4 days	+ 3	-
Glucantime BL09186	208	qd x 1 day	+11	87
		qd x 2 days	+ 7	84
		qd x 4 days	+ 4	85
		bid x 4 days	+ 5	93
	52	qd x 1 day	+11	38
		qd x 2 days	+ 3	51
		qd x 4 days	+ 4	64
		bid x 4 days	+ 3	68
	26	qd x 1 day	+ 4	17
		qd x 2 days	+ 8	43
		qd x 4 days	+ 5	63
		bid x 4 days	+ 3	53
Sinefungin BL58705	52	qd x 1 day	+10	87
		qd x 2 days	+ 9	87
		qd x 4 days	+ 4	90
		bid x 4 days	+ 1	91
	6.5	qd x 1 day	+ 9	73
		qd x 2 days	+10	77
		qd x 4 days	+ 6	85
		bid x 4 days	+ 3	76
	3.25	qd x 1 day	+ 8	47
		qd x 2 days	+ 8	67
		qd x 4 days	+ 4	73
		bid x 4 days	+ 5	70

*mg/kg

Appendix 2

Figure 1. Chemical structures of compounds found active in the primary visceral test system.



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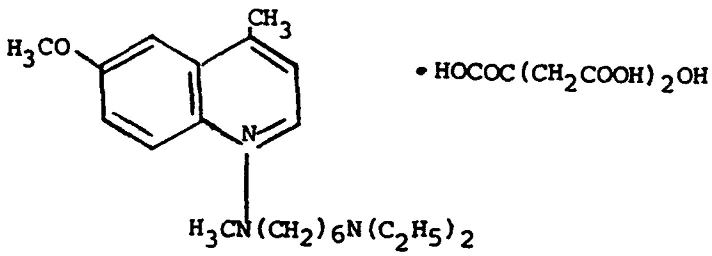

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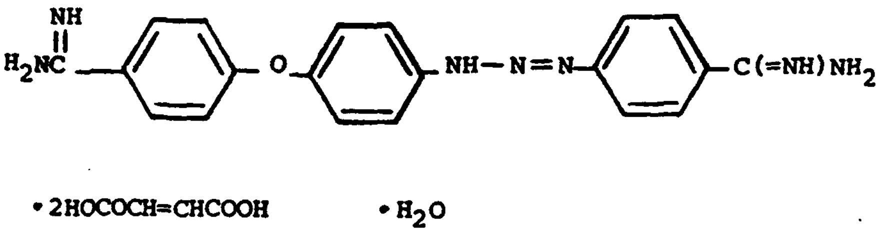

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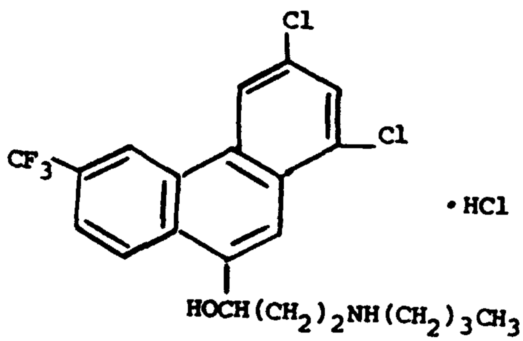

BK21070

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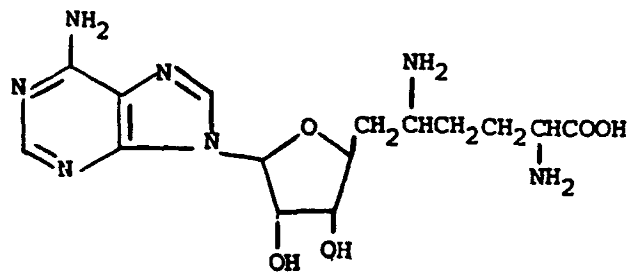

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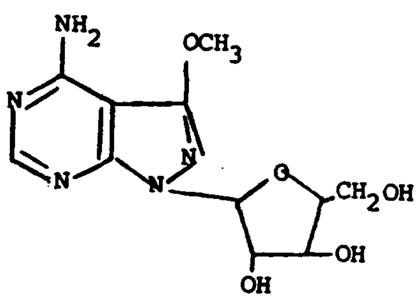

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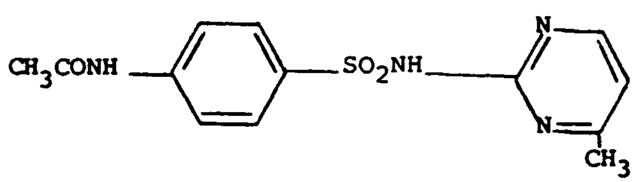
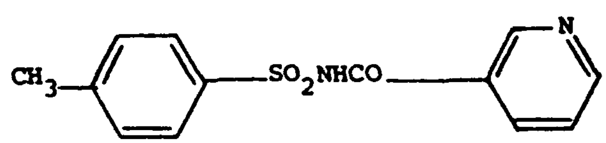


BL22876

AJ15304
PROPRIETARY

AR80315

PROPRIETARY



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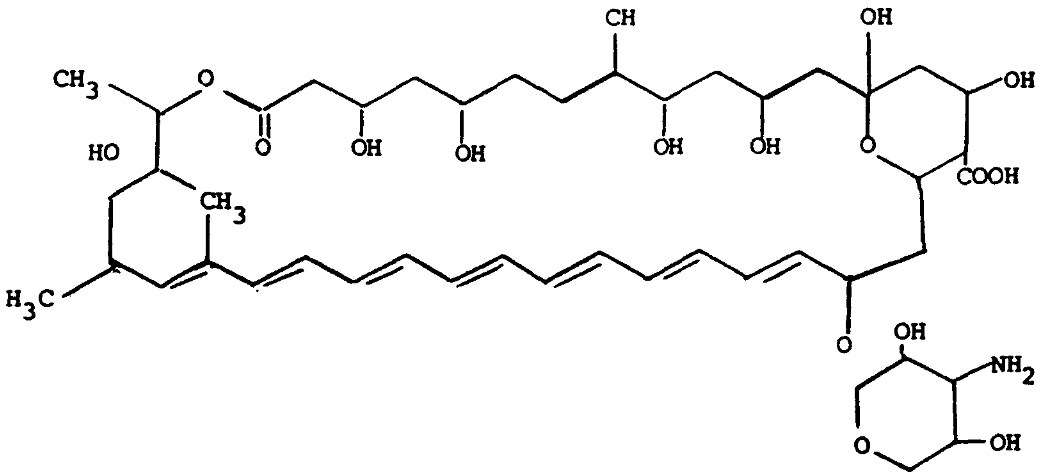

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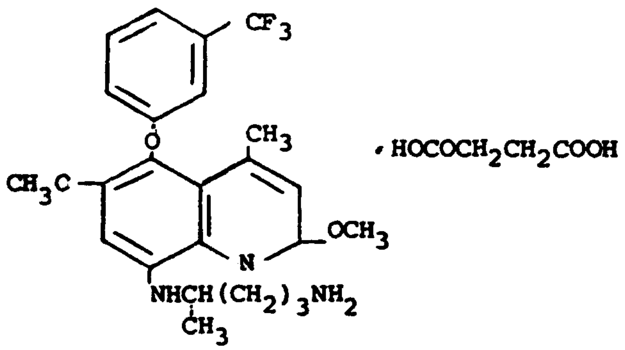

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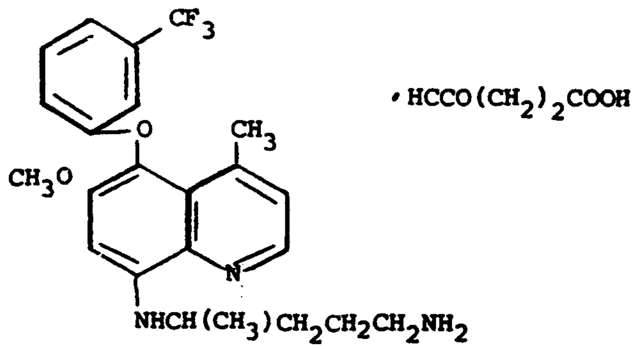

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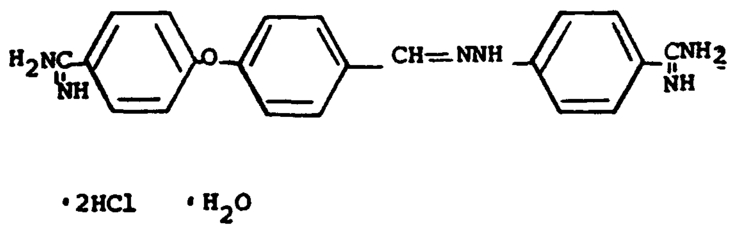

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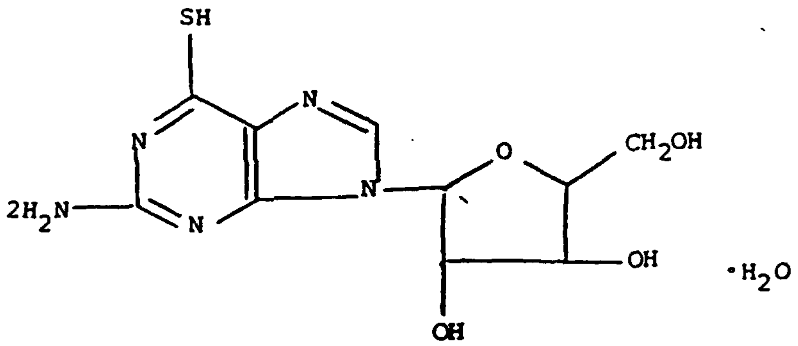

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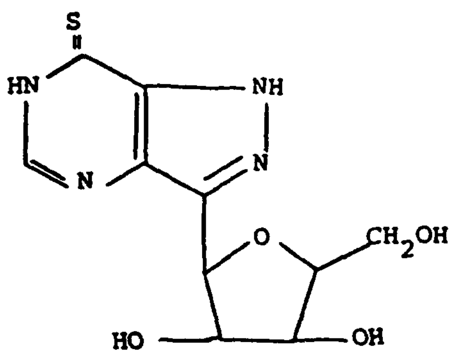

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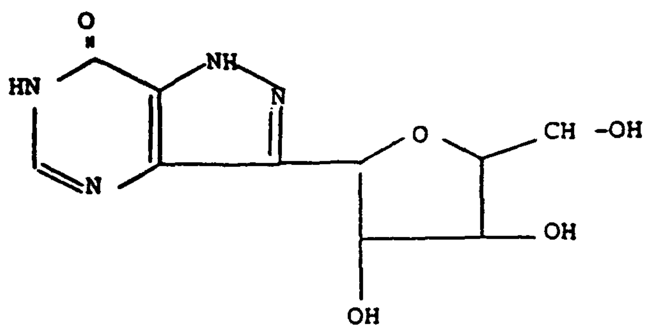

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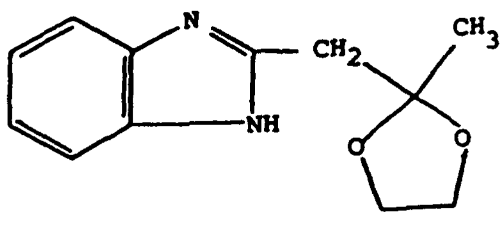

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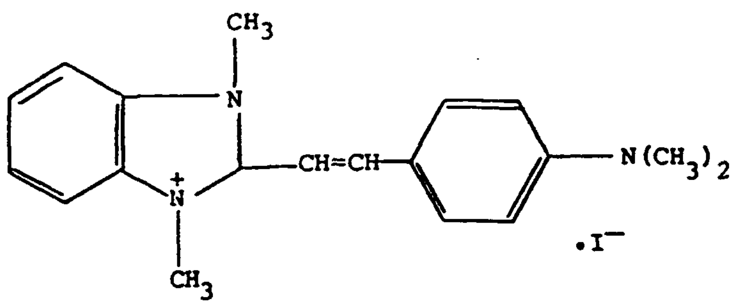

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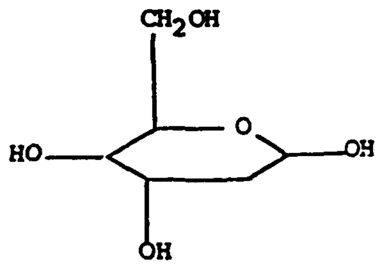

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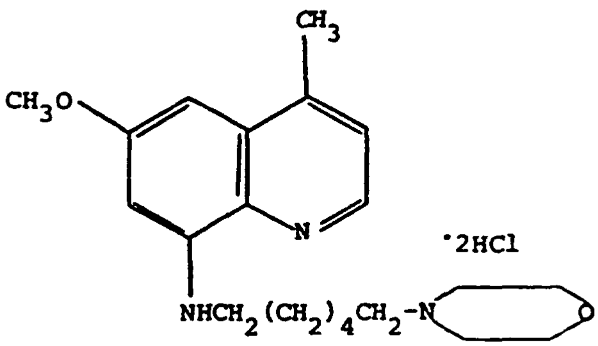

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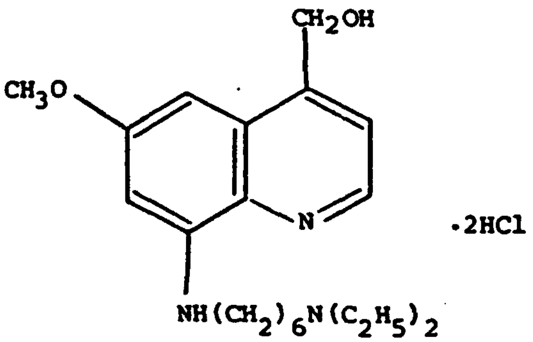

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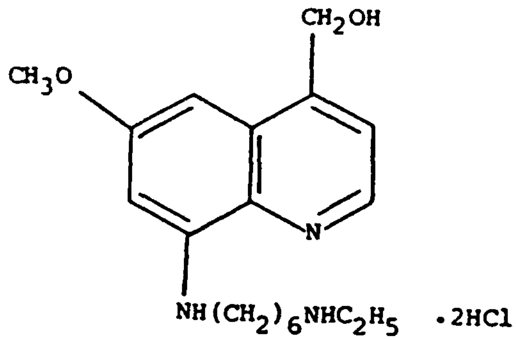

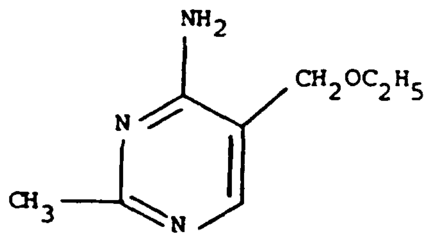

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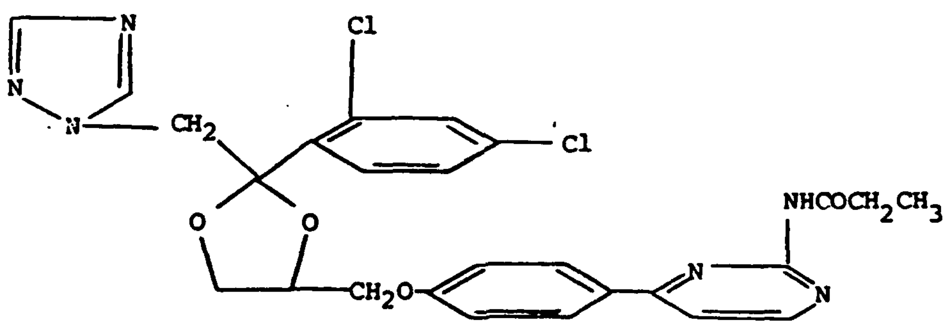

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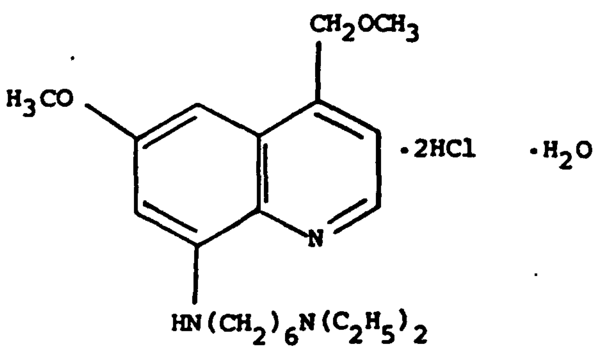

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BL50021

BL32550

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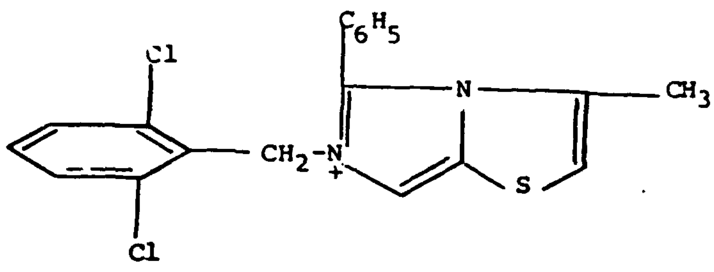

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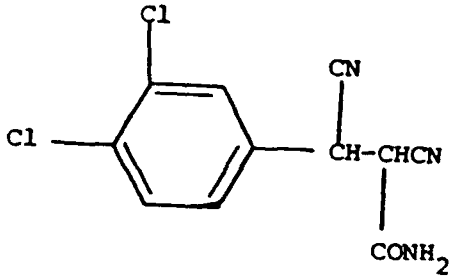

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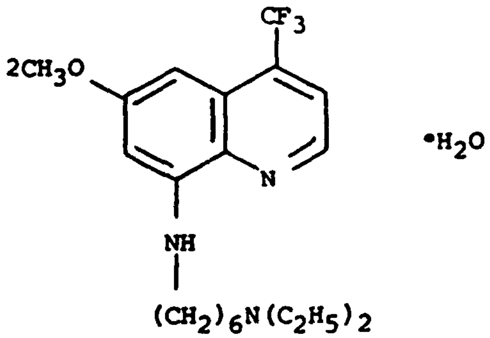

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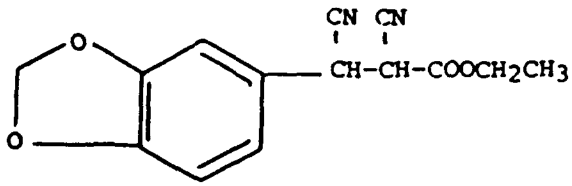

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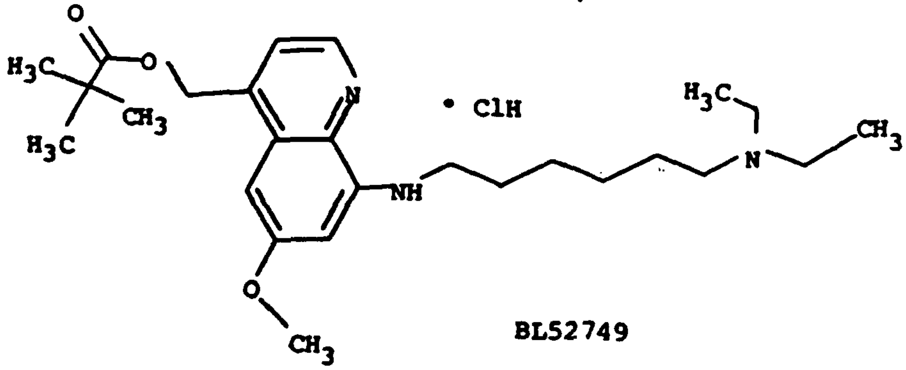

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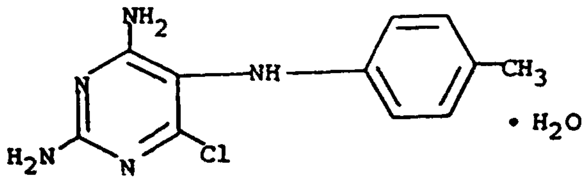
Figure 1. (Continued)



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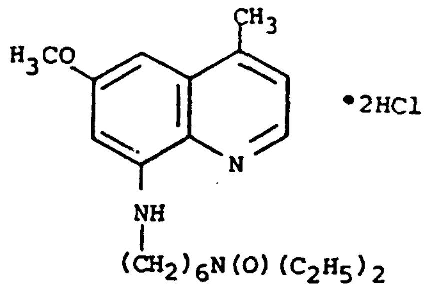

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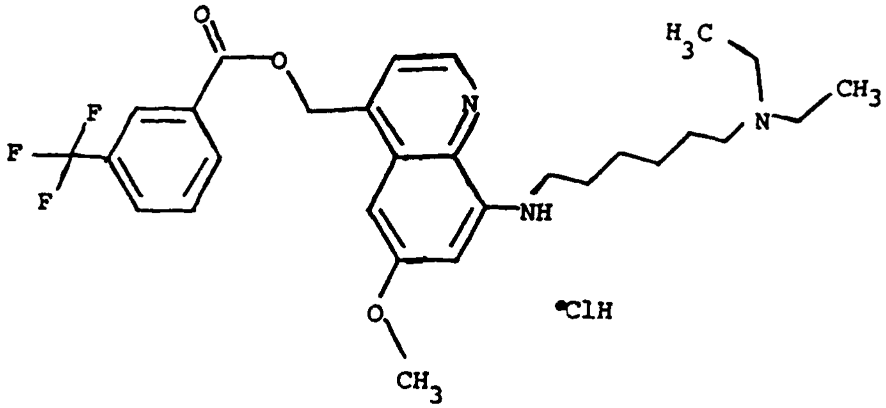

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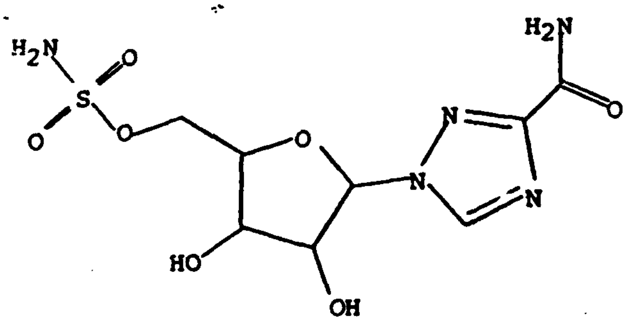

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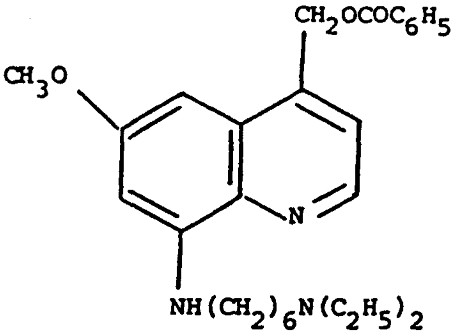
Figure 2. Chemical structures of WR06026 analogs.



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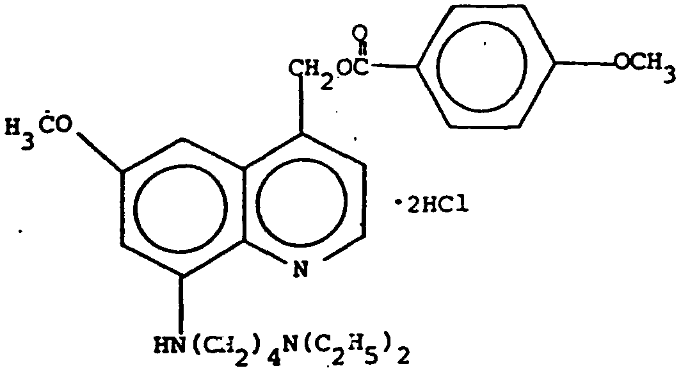

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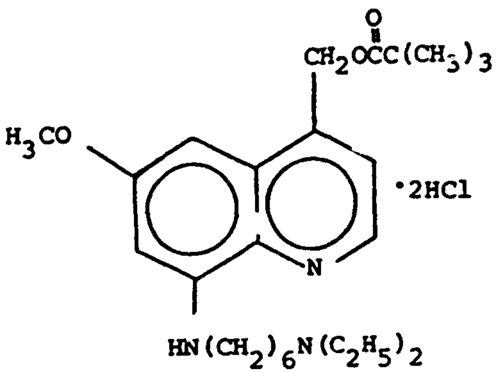

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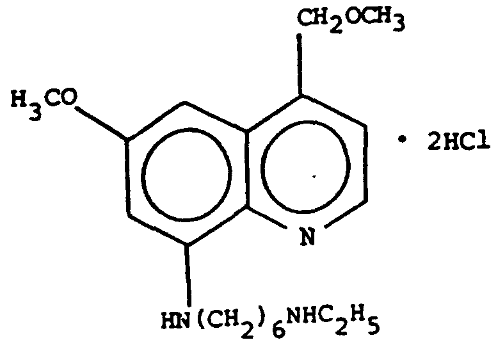

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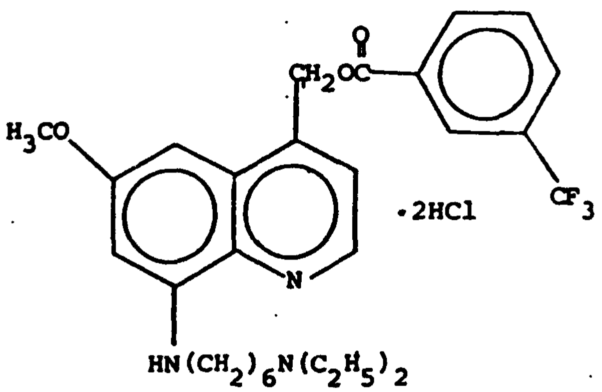

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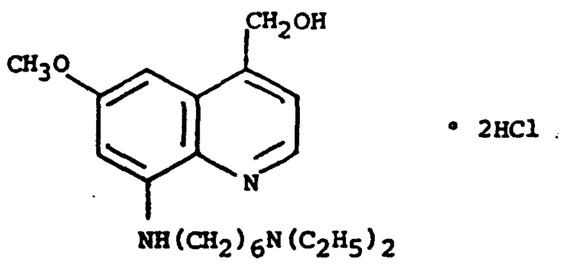
Figure 3. Structures of 8-aminoquinolines used in the study of the effect of route of administration on efficacy against *Leishmania donovani*.



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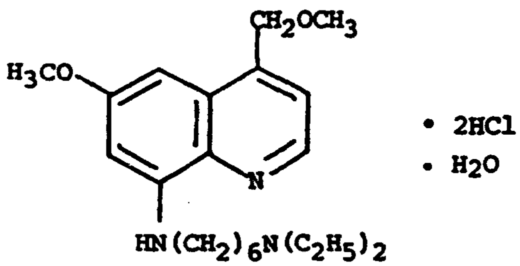

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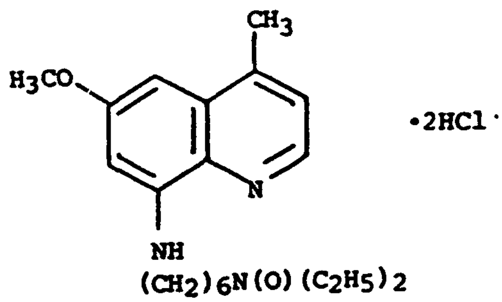

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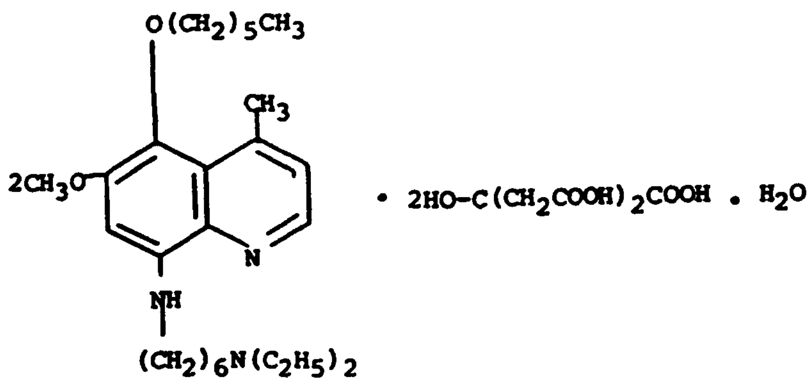

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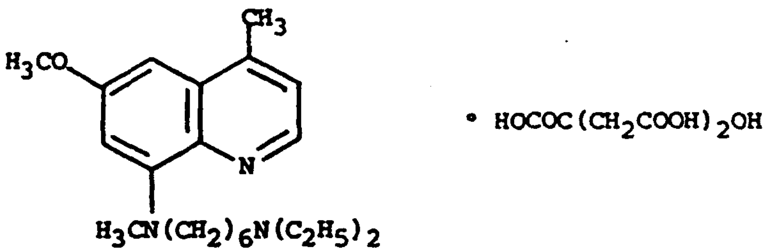
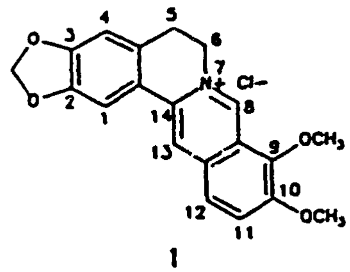
Figure 3. (Continued)



BK99121

BL03308
PROPRIETARY

Figure 4. Structures of berberine alkaloids.
(1) berberine chloride, (2) palmatine chloride, (3) oxyberberine, (4) dihydroberberine, (5) 8-cyanodihydroberberine, (6) tetrahydroberberine N-Oxide, (7) tetrahydroberberine, (8) N-methyltetrahydroberberinium iodide, (9) berberine betaine.



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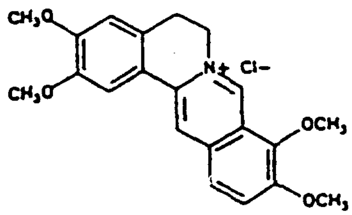

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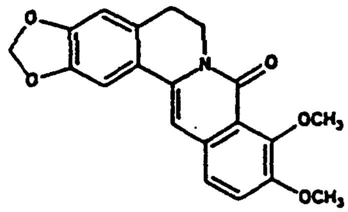

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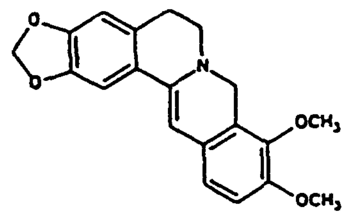

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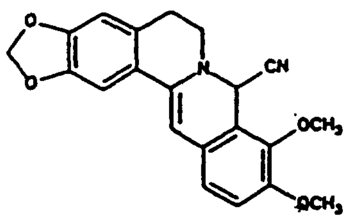

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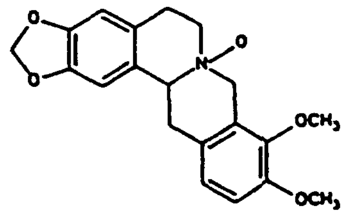

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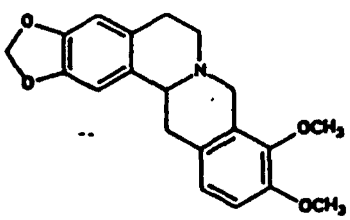

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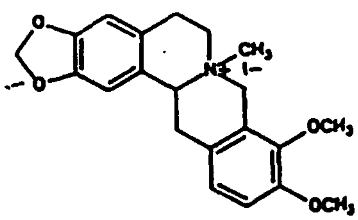

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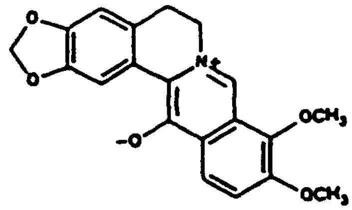

9

Appendix 3

April 10, 1990 - COL. 495
Gross pathologic observations in Experimental Hamsters as described by Dr. W. L. Chapman, Jr., DVM, Ph.D.

Group No.	Observations
1	No clinical signs
2	No clinical signs
3	No clinical signs
4	Torticollis; eyes sealed probably from inflammation; huddled in corner of cage; stooped; some have difficulty walking; some have discharge from eyes. Weight loss seen.
5	All of the signs seen in Group 4 except torticollis; weight loss seen.
6	All of the same signs as seen in Group 4 above. Some moribund; weight loss seen.
7	Mild torticollis; weight loss; possible photophobia.
8	Weight loss; roughened hair coat; possible photophobia.
9	Unilateral photophobia

Group	Percent weight change 24 hrs. after a single injection of MTP	Final percent weight change showed on computer printout
4	-9.22	-11
5	-7.05	- 6
6	-9.18	-10
7	-6.70	+ 3
8	-8.15	- 1
9	-7.64	+ 1

Infected: 4/2/90
Treatment: See Below
Necropsy: 4/16/90

COL 495

Treatment	MKD	Total mg/kg	Treatment Days	Gp. No.
Saline only	-	-	4/10-4/13	1
BL09186 only	52	208	4/10-4/13(Days 8-11)	2
Glucantime	13	52	4/10-4/13(Days 8-11)	3
MTP only	200μg	400μg	4/9(Day 7)+4/12(Day 10)	4
MTP + BL09186	200μg 52	400μg 208	4/9+4/12 4/10-4/13	5
MTP + BL09186	200μg 13	400μg 52	4/9+4/12 4/10-4/13	6
MTP only	100μg	200μg	4/9+4/12	7
MTP + BL09186	100μg 52	200μg 208	4/9+4/12 4/10-4/13	8
MTP + BL09186	100μg 13	200μg 52	4/9+4/12 4/10-4/13	9

Each group will contain 8 hamsters each. MTP administered IC. Glucantime and saline controls IM injections. Hamsters infected with 6,000,000 amastigotes.

Appendix 4

PERSONNEL EMPLOYED FROM THIS CONTRACT

Position and Name	Length of Employment
Research Coordinator II	
Waits, Virginia B.	01/01/85 - 01/15/91
Laboratory Technician II (full-time)	
Vance, Linda	05/06/85 - 03/04/86
Brown, Steve	03/04/86 - 07/02/87
Clements, Greg	03/01/85 - 06/30/86
Kimsey, Philip	07/17/86 - 06/30/88
Bloodworth, Richard	07/11/88 - 09/01/89
Laboratory Technician II (part-time)	
Batra, Nam	07/01/85 - 01/09/86
Barnard, David	01/23/87 - 03/23/90
Ekanayake, Sriyani	12/15/87 - 06/30/90
Shin, Sung Shik	12/15/87 - 08/31/89
Data Entry Operator	
Shadwell, Dina	09/23/85 - 01/14/88
Waits, Eric	06/13/85 - 09/24/87

BIBLIOGRAPHY OF PUBLISHED WORK

1. Berman, J. D., W. L. Hanson, W. L. Chapman, Jr., Alving, and G. Lopez-Berestein. 1986. Antileishmanial activity of liposome-encapsulated amphotericin B in the hamster and monkey. Antimicrobial Agents and Chemother. 30: 847-851

2. Berman, J. D., W. L. Hanson, J. K. Lovelace, V. B. Waits, J. E. Jackson, W. L. Chapman, Jr., and R. S. Klein. 1987. Activity of purine analogs against Leishmania donovani in vivo. Antimicrobial Agents and Chemother. 31(1): 111-113.

3. Vennerstrom, J. L., J. K. Lovelace, V. B. Waits, W. L. Hanson, and D. L. Klayman. 1990. Berberine Derivatives as Antileishmanial Drugs. Antimicrobial Agents and Chemother. 34: 918-921.

GRADUATE DEGREES RESULTING FROM THIS CONTRACT

None

END

FILMED

DATE: 8-92

DTIC